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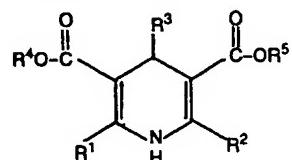
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㉚ Novel dihydropyridine derivatives and process for preparing the same.

㉛ Dihydropyridine derivatives and salts thereof represented  
by the general formula,



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which possess excellent calcium antagonist effect, hypotensive effect, platelets aggregation inhibitory effect, phosphodiesterase inhibitory effect, calmodulin inhibitory effect and peroxidized lipid lowering effect, and thus dihydropyridine derivatives and salts thereof are useful as a coronary blood flow improving agent such as coronary vasodilator, hypotensive agent, prophylaxis and treating agents for thrombosis, phosphodiesterase inhibitory agent, peroxidized lipid metabolism lowering agent, anti-inflammatory agent and others.

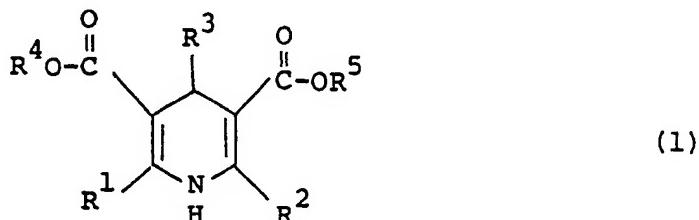
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NOVEL DIHYDROPYRIDINE DERIVATIVES  
AND PROCESS FOR PREPARING THE SAME

1 FIELD OF THE INVENTION

The present invention relates to dihydro-pyridine derivatives and salts thereof. More particularly, the present invention relates to dihydropyridine derivatives and salts thereof, process for preparing the same, as well as pharmaceutical composition containing the same as the active ingredient.

The dihydropyridine derivatives and salts thereof are novel compounds, and are not known in any of prior art references. The dihydropyridine derivatives and salts thereof according to the present invention are represented by the general formula (1),



wherein R<sup>1</sup> and R<sup>4</sup> are each a lower alkyl group; R<sup>2</sup> is a lower alkyl group or a group of the formula -CH<sub>2</sub>-A-R<sup>6</sup>  
15 [wherein A is a straight-chain or branched-chain unsaturated group hydrocarbon group which may have an oxygen atom or a group of the formula -N-R<sup>7</sup> (wherein R<sup>7</sup> is a lower alkyl group); and R<sup>6</sup> is a phenyl group which may have a hydroxyl group]; R<sup>3</sup> is a phenyl group which

- 1 may have 1 to 2 substituents selected from the group consisting of a nitro group, a lower alkyl group which may have 1 to 3 halogen atoms, a lower alkoxy group and a halogen atom; and  $R^5$  is a lower alkyl group, a 1,2,3,6-
- 5 tetrahydropyridyl-lower alkyl group which may have, as the substituent, a phenyl group which may have halogen atoms or lower alkyl groups as the substituents on the phenyl ring, or a group of the formula  $-CH_2-A'-R^8$  [wherein  $A'$  is a straight-chain or branched-chain unsaturated
- 10 hydrocarbon group which may have or may not have an oxygen atom, a sulfur atom, a group of the formula  $-N-R^7$  (wherein  $R^7$  is a lower alkyl group) or a group of the formula  $-N\text{ } \text{ } N-$  in the unsaturated hydrocarbon group; and  $R^8$  is a phenyl group which may have 1 to 3 substituents
- 15 selected from the group consisting of a lower alkoxy group, a halogen atom, a lower alkylthio group, a hydroxyl group, a lower alkanoyloxy group, a tetrahydro-pyranloxy group and a lower alkoxy-lower alkoxy group; a pyridyl group; a thienyl group; furyl group, or a
- 20 tetrazolyl group which may have a lower alkyl group as the substituent]; provided that when  $R^5$  is a lower alkyl group, then  $R^2$  should be a group of the formula  $-CH_2-A-R^6$  (wherein  $A$  and  $R^6$  are the same as defined above).

Dihydropyridine derivatives and salts thereof

- 25 represented by the general formula (1) possess excellent calcium antagonist effect, hypotensive effect, platelets aggregation inhibitory effect, phosphodiesterase inhibitory effect, calmodulin inhibitory effect and

1 peroxidized lipid lowering effect, and thus the dihydro-  
pyridine derivative and salt thereof represented by the  
general formula (1) are useful as a coronary blood flow  
improving agent such as coronary vasodilator, hypotensive  
5 agent, prophylaxis and treating agents for thrombosis,  
phosphodiesterase inhibitory agent, peroxidized lipid  
metabolism lowering agent, anti-inflammatory agent and  
others.

DESCRIPTION OF THE PRIOR ART

10 Compounds similar to the dihydropyridine  
derivatives according to the present invention are known  
from the disclosures in Japanese Patent Application Kokai  
(Laid-open) No. 51-108075 (1976) and Japanese Patent  
Application Kokai (Laid-open) No. 56-36455 (1981). Com-  
15 pounds of these prior art references are known as useful  
hypotensive agents, peripheral and cerebral vasodilating  
agents and treating agent for coronary blood vessels.  
On the contrary, dihydropyridine derivatives according  
to the present invention have features in that they  
20 perform their pharmacological effects for longer period  
of time with less side-effects as compared with known  
compounds. Furthermore, dihydropyridine derivatives  
according to the present invention are useful as carcino-  
static agents.

25 SUMMARY OF THE INVENTION

An object of the present invention is to provide

1 novel dihydropyridine derivatives.

Another object of the present invention is to provide process for preparing said dihydropyridine derivatives.

5 Further object of the present invention is to provide a pharmaceutical composition containing said dihydropyridine derivative as the active ingredient.

These and other objects and features of the present invention will become more fully apparent from  
10 the following description.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Dihydropyridine derivatives represented by the general formula (1) according to the present invention, examples of various substituents as defined in R<sup>1</sup>, R<sup>2</sup>,  
15 R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, A and A' are as follows.

As to the lower alkyl group, an alkyl group having 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl groups and others can be exemplified.

20 As to the lower alkyl group which may have halogen atoms as the substituents, an alkyl group having 1 to 6 carbon atoms which may have 1 to 3 halogen atoms as the substituents, in addition to the above-mentioned alkyl groups having 1 to 6 carbon atoms, trifluoromethyl,  
25 2,2-difluoroethyl, 1,1-dichloroethyl, trichloromethyl, dichloromethyl, tribromomethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2-chloroethyl, 1,2-dichloroethyl,

- 1 3,3,3-trichloropropyl, 3-fluoropropyl, 4-chlorobutyl, 3-chloro-2-methylethyl groups and others can be exemplified.

As to the lower alkoxy group, an alkoxy group having 1 to 6 carbon atoms such as methoxy, ethoxy,

- 5 propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy groups and others can be exemplified.

As to the halogen atom, fluorine atom, chlorine atom, bromine atom and iodine atom can be exemplified.

- 10 As to the lower alkoxy-lowered alkoxy group,  
an alkoxyalkoxy group of which the alkoxy moieties having  
1 to 6 carbon atoms such as methoxymethoxy, 2-methoxy-  
ethoxy, 1-methoxyethoxy, 3-methoxypropoxy, 4-methoxybutoxy,  
1,1-dimethyl-2-methoxyethoxy, 5-methoxypentyloxy, 6-  
methoxyhexyloxy, 2-methyl-3-methoxypropoxy, ethoxymethoxy,  
15 3-ethoxypropoxy, 6-ethoxyhexyloxy, 2-propoxyethoxy, 4-  
propoxybutoxy, 5-butoxypentyloxy, pentyloxymethoxy, 1-  
pentyloxyethoxy, 1,1-dimethyl-2-hexyloxyethoxy, 3-  
hexyloxypropoxy groups and others can be exemplified.

- 20 As to the lower alkylthio group, an alkylthio group having 1 to 6 carbon atoms, such as methylthio,  
ethylthio, propylthio, isopropylthio, butylthio, tert-butylthio, pentylthio, hexylthio groups and others can  
be exemplified.

- 25 As to the lower alkanoyloxy group, an alkanoyloxy group having 1 to 6 carbon atoms, such as formyloxy,  
acetyloxy, propionyloxy, butyryloxy isobutyryloxy, penta-  
noyloxy, tert- butyryloxy, hexanoyloxy groups and others  
can be exemplified.

1 As to the phenyl group which may have 1 to 3 substituents selected from the group consisting of a lower alkoxy group, a halogen atom, a lower alkylthio group, a hydroxyl group, a lower alkanoyloxy group, a tetra-  
5 hydropyranyloxy group and a lower alkoxy-lower alkoxy group, a phenyl group which may have 1 to 3 substituents selected from the group consisting of an alkoxy group having 1 to 6 carbon atoms, a halogen atom, an alkylthio group having 1 to 6 carbon atoms, a hydroxyl group, an  
10 alkanoyloxy group having 1 to 6 carbon atoms, a tetrahydropyranyloxy group and an alkoxyalkoxy group of which alkoxy moieties having 1 to 6 carbon atoms, such as phenyl, 2-, 3- or 4-chlorophenyl, 2-, 3- or 4-fluoro-phenyl, 2-, 3- or 4-bromophenyl, 2-, 3- or 4-iodophenyl,  
15 3,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,5-dibromophenyl, 2-, 3- or 4-methyl-thiophenyl, 2-, 3- or 4-ethylthiophenyl, 4-propylthio-phenyl, 3-isopropylthiophenyl, 2-butylthiophenyl, 4-hexylthiophenyl, 3-pentylthiophenyl, 4-tert-butylthio-  
20 phenyl, 3,4-dimethylthiophenyl, 2,5-dimethylthiophenyl, 2-, 3- or 4-methoxyphenyl, 2-, 3- or 4-ethoxyphenyl, 3-propoxyphenyl, 4-isopropoxyphenyl, 3-butoxyphenyl, 2-pentyloxyphenyl, 4-tert-butoxyphenyl, 4-hexyloxyphenyl, 3,4-dimethoxyphenyl, 3,4-diethoxyphenyl, 2,5-dimethoxy-  
25 phenyl, 2-, 3- or 4-(2-tetrahydropyranyloxy)phenyl, 2,4-bis(2-tetrahydropyranyloxy)phenyl, 3-methylthio-4-chlorophenyl, 2-chloro-6-methylthiophenyl, 2-methoxy-3-

- 1 hydroxyphenyl, 3,4,5-trimethoxyphenyl, 3,4,5-trimethyl-thiophenyl, 3,4,5-trichlorophenyl, 2-, 3- or 4-hydroxy-phenyl, 3,4-dihydroxyphenyl, 2,6-dihydroxyphenyl, 3,4,5-trihydroxyphenyl, 2-, 3- or 4-acetoxyloxyphenyl, 4-propio-
- 5 nyloxyphenyl, 3-isopropionyloxyphenyl, 2-butyryloxy-phenyl, 4-hexanoyloxyphenyl, 3-pentanoyloxyphenyl, 4-tert-butyryloxyphenyl, 3,4-diacetyloxyphenyl, 2,5-diacetyloxyphenyl, 3,4,5-tridiacetyloxyphenyl, 2-methoxy-methoxyphenyl, 3-(2-methoxyethoxy)phenyl, 4-(1-methoxy-
- 10 ethoxy)phenyl, 2-(3-methoxypropoxy)phenyl, 3-(4-methoxybutoxy)phenyl, 4-(1,1-dimethyl-2-methoxyethoxy)-phenyl, 2-(5-methoxypentyloxy)phenyl, 3-(6-methoxy-hexyloxy)phenyl, 4-(2-methyl-3-methoxypropoxy)phenyl, 2-(ethoxymethoxy)phenyl, 3-(3-ethoxypropoxy)phenyl,
- 15 4-(6-ethoxyhexyloxy)phenyl, 2-(2-propoxyethoxy)phenyl, 3-(4-propoxybutoxy)phenyl, 4-(5-butoxypentyloxy)phenyl, 2-(pentyloxymethoxy)phenyl, 3-(1-pentyloxyethoxy)phenyl, 4-(1,1-dimethyl-2-hexyloxyethoxy)phenyl, 2-(3-hexyloxy-propoxy)phenyl, 2-(3-hexyloxypropoxy)phenyl groups and
- 20 others can be exemplified.

As to the phenyl group which may have 1 to 2 substituents selected from the group consisting of a nitro group, a lower alkyl group which may have 1 to 3 halogen atoms, a lower alkoxy group and a halogen atom,

- 25 a phenyl group which may have 1 to 2 substituents, on the phenyl ring, selected from the group consisting of a nitro group, an alkyl group having 1 to 6 carbon atoms

- 1 which may have 1 to 3 halogen atoms, an alkoxy group having 1 to 6 carbon atoms, and a halogen atom, such as a phenyl, 2-, 3- or 4-chlorophenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-bromophenyl, 2-, 3- or 4-iodophenyl,
- 5 3,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 2,4-dichlorophenyl, 3,4-difluorophenyl, 3,5-dibromophenyl, 2-, 3- or 4-nitrophenyl, 2,4-dinitrophenyl, 2,6-dinitrophenyl, 3,4-dinitrophenyl, 3,5-dinitrophenyl, 2-, 3- or 4-methoxyphenyl, 2-, 3- or 4-ethoxyphenyl, 3-
- 10 propoxyphenyl, 4-isopropoxyphenyl, 3-butoxyphenyl, 2-pentyloxyphenyl, 4-tert-butoxyphenyl, 4-hexyloxyphenyl, 3,4-dimethoxyphenyl, 3,4-diethoxyphenyl, 2,5-dimethoxyphenyl, 2-, 3- or 4-methylphenyl, 2-, 3- or 4-ethylphenyl, 4-propylphenyl, 3-isopropylphenyl, 2-butylphenyl, 4-
- 15 hexylphenyl, 3-pentylphenyl, 4-tert-butylphenyl, 3,4-dimethylphenyl, 2,5-dimethylphenyl, 2-(trifluoromethyl)phenyl, 3-(2,3-difluoroethyl)phenyl, 4-(1,1-dichloroethyl)phenyl, 3-(trichloromethyl)phenyl, 2-(dichloromethyl)phenyl, 4-(tribromomethyl)phenyl, 3-(2,2,2-trifluoroethyl)phenyl, 2-(2-chloroethyl)phenyl, 4-(1,2-dichloroethyl)phenyl, 3-(3,3,3-trichloropropyl)phenyl, 4-(3-chloro-2-methylethyl)phenyl, 3-(4-chlorobutyl)phenyl, 2-(3-fluoropropyl)phenyl, 3-methyl-4-chlorophenyl, 2-chloro-6-methylphenyl and 2-methoxy-3-nitrophenyl groups and others
- 20 25 can be exemplified.

As to the 1,2,4,6-tetrahydropyridyl-lower alkyl group which may have, as the substituent, a phenyl group which may have halogen atoms or lower alkyl groups as

- 1 the substituents on the phenyl ring, a 1,2,3,6-tetrahydropyridyl group substituted-alkyl group having 1 to 6 carbon atoms in the alkyl moiety, which may have as the substituent, a phenyl group which may have halogen atoms
- 5 or alkyl groups having 1 to 6 carbon atoms, as the substituents on the phenyl ring, such as 1,2,3,6-tetrahydropyridylmethyl, 2-(1,2,3,6-tetrahydropyridyl)ethyl, 1-(1,2,3,6-tetrahydropyridyl)ethyl, 3-(1,2,3,6-tetrahydropyridyl)propyl, 4-(1,2,3,6-tetrahydropyridyl)butyl,
- 10 1,1-dimethyl-2-(1,2,3,6-tetrahydropyridyl)ethyl, 5-(1,2,3,6-tetrahydropyridyl)pentyl, 6-(1,2,3,6-tetrahydropyridyl)hexyl, 2-methyl-3-(1,2,3,6-tetrahydropyridyl)-propyl, (4-phenyl-1,2,3,6-tetrahydropyridyl)methyl, 2-[4-(2-fluorophenyl)-1,2,3,6-tetrahydropyridyl]ethyl,
- 15 1-[4-(3-bromophenyl)-1,2,3,6-tetrahydropyridyl]ethyl, 3-[3-(4-chlorophenyl)-1,2,3,6-tetrahydropyridyl]propyl, [4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridyl]methyl, [4-(4-methylphenyl)-1,2,3,6-tetrahydropyridyl]methyl, [4-(2-(2-ethylphenyl)-1,2,3,6-tetrahydropyridyl]methyl,
- 20 1,1-dimethyl-2-[3-(3-propylphenyl)-1,2,3,6-tetrahydropyridyl]ethyl, 5-[2-(2-tert-butylphenyl)-1,2,3,6-tetrahydropyridyl]pentyl, 6-[3-(4-pentylphenyl)-1,2,3,6-tetrahydropyridyl]hexyl, and 2-methyl-3-[4-(3-hexylphenyl)-1,2,3,6-tetrahydropyridyl]propyl groups and others can
- 25 be exemplified.

As to the straight-chain or branched-chain unsaturated hydrocarbon residual group which may have or may not have an oxygen atom, a sulfur atom, a group of

- 1 the formula  $-N-R^7$  (wherein  $R^7$  is a lower alkyl group) or  
a group of the formula  $-N\text{ } \text{ } N-$  in the unsaturated  
hydrocarbon residual group, a straight-chain or branched-  
chain unsaturated hydrocarbon residual group having 2 to  
5 6 carbon atoms in the unsaturated hydrocarbon residual  
moiety, having 1 to 3 double bonds and/or triple bonds  
therein, said unsaturated hydrocarbon residual group  
may have or may not have an oxygen atom, a sulfur atom,  
a group of the formula  $-N-R^7$  (wherein  $R^7$  is an alkyl  
10 group having 1 to 6 carbon atoms), or a group of the  
formula  $-N\text{ } \text{ } N-$ , such as vinylene, 1-propenylene, 1-  
methyl-1-propenylene, 2-methyl-1-propenylene, 2-propenyl-  
lene, 2-butenylene, 1-butenylene, 3-butenylene, 2-  
pentenylene, 1-pentenylene, 3-pentenylene, 4-pentenylene,  
15 1,3-butadienylene, 1,3-pentadienylene, 2-penten-4-ylene,  
2-hexenylene, 1-hexenylene, 5-hexenylene, 3-hexenylene,  
4-hexenylene, 3,3-dimethyl-1-propenylene, 2-ethyl-1-  
propenylene, ethynylene, 2-propynylene, 1-propynylene,  
1,1-dimethyl-2-propynylene, 3,3-dimethyl-1-propynylene,  
20 2-butynylene, 3-butynylene, 1-butynylene, 2-pentyne,  
1-pentyne, 3-pentyne, 4-pentyne, 2-hexyne,  
1-hexyne, 3-hexyne, 4-hexyne, 5-hexyne,  
1,3-hexadienylene, 1,4-hexadienylene, 1,3,5-hexatrienylene,  
1-propyleneoxy, 1-methyl-1-propyleneoxy, 2-methyl-1-  
25 propyleneoxy, 2-propyleneoxy, 2-butenyleneoxy, 1-  
propyleneoxymethylene, 1-butenyleneoxy, 3-butenyleneoxy,  
2-pentenyleneoxy, 1-pentenyleneoxy, 3-pentenyleneoxy,  
4-pentenyleneoxy, 1,3-butadienyleneoxy, 1,3-pentadienylene-

- 1 oxy, 2-penten-4-yleneoxy, 2-hexenyleneoxy, 1-hexenyleneoxy, 5-hexenyleneoxy, 3-hexenyleneoxy, 4-hexenyleneoxy, 3,3-dimethyl-1-propenyleneoxy, 2-ethyl-1-propenyleneoxy, ethynyleneoxy, 2-propynyleneoxy, 1-propynyleneoxy, 1,1-
- 5 dimethyl-2-propynyleneoxy, 3,3-dimethyl-1-propynyleneoxy, 3-butynyleneoxy, 1-butynyleneoxy, 2-pentynyleneoxy, 1-pentynyleneoxy, 3-pentynyleneoxy, 4-pentynyleneoxy, 2-hexynyleneoxy, 1-hexynyleneoxy, 3-hexynyleneoxy, 4-hexynyleneoxy, 5-hexynyleneoxy, 1,3-hexadienyleneoxy, 1,4-
- 10 hexadienyleneoxy, 1,3,5-hexatrienyleneoxy, 1-propenyleneoxyethylene, 1-propenyleneoxypropylene, 1-methyl-1-propenyleneoxymethylene, 2-methyl-1-propenyleneoxyethylene, 2-propenyleneoxypropylene, 2-butenyleneoxymethylene, 1-butenyleneoxyethylene, 2-pentenyleneoxymethylene,
- 15 1,3-butadienyleneoxymethylene, 1,3-pentadienyleneoxy-methylene, 1-propynyleneoxymethylene, 2-propynyleneoxyethylene, ethynyleneoxymethylene, 3-butynyleneoxymethylene, 1-butynyleneoxyethylene, 1-pentynyleneoxymethylene, 3,3-dimethyl-1-propynyleneoxymethylene, 1-
- 20 propenylenethio, 1-methyl-1-propenylenethio, 2-methyl-1-propenylenethio, 2-propenylenethio, 2-butenylenethio, 1-propenylenethiomethylene, 1-butenylenethio, 3-butenylene-thio, 2-pentenylenethio, 1-pentenylenethio, 3-pentenylenethio, 4-pentenylenethio, 1,3-butadienylenethio, 1,3-
- 25 pentadienylenethio, 2-penten-4-ylenethio, 2-hexenylene-thio, 1-hexenylenethio, 5-hexenylenethio, 3-hexenylene-thio, 4-hexenylenethio, 3,3-dimethyl-1-propenylenethio, 2-ethyl-1-propenylenethio, ethynylenethio, 2-propynylenethio,

- 1 1-propynylidenethio, 1,1-dimethyl-2-propynylidenethio, 3,3-dimethyl-1-propynylidenethio, 3-butynylidenethio, 1-butynylene-thio, 2-pentynylidenethio, 1-pentynylidenethio, 3-pentynylene-thio, 4-pentynylidenethio, 2-hexynylidenethio, 1-hexynylene-thio, 3-hexynylidenethio, 4-hexynylidenethio, 5-hexynylene-thio, 1,3-hexadienylenethio, 1,4-hexadienylenethio, 1,3,5-hexatrienylenethio, 1-propenylidenethioethylene, 1-propenylidenethiopropylene, 1-methyl-1-propenylidenethiomethylene, 2-methyl-1-propenylidenethioethylene, 2-propenylidenethiopropylene, 2-butenylidenethiomethylene, 1-butenylidenethioethylene, 2-pentenylidenethiomethylene, 1,3-butadienylenethiomethylene, 1,3-pentadienylenethiomethylene, 1-propynylidenethiomethylene, 2-propynylethioethylene, ethynylidenethiomethylene, 3-butynylene-thiomethylene, 1-butynylidenethioethylene, 1-pentynylene-thiomethylene, 3,3-dimethyl-1-propynylidenethiomethylene, N-methyl-N-(1-propenylene)amino, N-ethyl-N-(1-methyl-1-propenylene)amino, N-propyl-N-(2-methyl-1-propenylene)amino, N-n-butyl-N-(2-propenylene)amino, N-pentyl-N-(2-butenylene)amino, N-methyl-N-(1-propenylene)aminomethylene, N-hexyl-N-(1-butenylene)amino, N-methyl-N-(3-butenylene)amino, N-ethyl-N-(2-pentenylene)amino, N-propyl-N-(1-pentenylene)amino, N-tert-butyl-N-(3-pentenylene)amino, N-pentyl-N-(4-pentenylene)amino, N-hexyl-N-(1,3-butadienylene)amino, N-methyl-N-(1,3-pentadienylene)amino, N-ethyl-N-(2-penten-4-ylnylene)amino, N-propyl-N-(2-hexenylene)amino, N-n-butyl-N-(1-hexenylene)amino, N-pentyl-N-(5-hexenylene)-

- 1 amino, N-hexyl-N-(3-hexenylene)amino, N-methyl-N-(1-propynylene)amino, N-ethyl-N-(1,1-dimethyl-2-propynylene)amino, N-propyl-N-(3,3-dimethyl-1-propynylene)-amino, N-tert-butyl-N-(3-butynylene)amino, N-pentyl-N-(1-butynylene)amino, N-hexyl-N-(2-pentynylene)amino, N-methyl-N-(1-pentynylene)amino, N-ethyl-N-(3-pentynylene)-amino, N-propyl-N-(4-pentynylene)amino, N-butyl-N-(2-hexynylene)amino, N-pentyl-N-(1-hexynylene)amino, N-hexyl-N-(3-hexynylene)amino, N-methyl-N-(4-hexynylene)-amino, N-ethyl-N-(5-hexynylene)amino, N-propyl-N-(1,3-hexadienylene)amino, N-tert-butyl-N-(1,4-hexadienylene)-amino, N-pentyl-N-(1,3,5-hexatrienylene)amino, N-hexyl-N-(1-propenylene)aminoethylen, N-methyl-N-(1-propenylene)-aminopropylene, N-ethyl-N-(1-methyl-1-propenylene)-aminomethylene, N-propyl-N-(2-methyl-1-propenylene)-aminoethylene, N-butyl-N-(2-propenylene)aminomethylene, N-pentyl-N-(2-butenylene)aminomethylene, N-hexyl-N-(1-butenylene)aminoethylene, N-methyl-N-(2-pentenylene)-aminomethylene, N-ethyl-N-(1,3-butadienylene)amino-methylene, N-propyl-N-(1,3-pentadienylene)aminomethylene, N-methyl-N-(1-propynylene)aminomethylene, N-butyl-N-(2-propynylene)aminoethylene, N-pentyl-N-ethynylene-aminomethylene, N-hexyl-N-(3-butynylene)aminomethylene, N-methyl-N-(1-butynylene)aminoethylene, N-ethyl-N-(1-pentynylene)aminoethylene, N-methyl-N-(3,3-dimethyl-1-propynylene)aminomethylene, 4-(1-propenylene)-1-piperazinyl, 4-(1-methyl-1-propenylene)-1-piperazinyl, 4-(2-methyl-1-propenylene)-1-piperazinyl, 4-(2-propenylene)-1-piperazinyl,

- 1 4-(2-butenylene)-1-piperazinyl, 4-(1-propenylene)-1-piperazinylmethylen, 4-(1-butenylene)-1-piperazinyl, 4-(3-butenylene)-1-piperazinyl, 4-(2-pentenylene)-1-piperazinyl, 4-(1-pentenylene)-1-piperazinyl, 4-(3-pentenylene)-1-piperazinyl, 4-(4-pentenylene)-1-piperazinyl, 4-(1,3-butadienylene)-1-piperazinyl, 4-(1,3-pentadienylene)-1-piperazinyl, 4-(2-penten-4-ynylene)-1-piperazinyl, 4-(2-hexenylene)-1-piperazinyl, 4-(1-hexenylene)-1-piperazinyl, 4-(5-hexenylene)-1-piperazinyl, 4-(1-butynylene)-1-piperazinylethylene, 4-(1-pentynylene)-1-piperazinylmethylen, 4-(3,3-dimethyl-1-propynylene)-1-piperazinylmethylen, 4-(3-hexenylene)-1-piperazinyl, 4-(4-hexenylene)-1-piperazinyl, 4-(3,3-dimethyl-1-propenylene)-1-piperazinyl, 4-(2-ethyl-1-propenylene)-1-piperazinyl, 4-(ethynylene)-1-piperazinyl, 4-(2-propynylene)-1-piperazinyl, 4-(1-propynylene)-1-piperazinyl, 4-(1,1-dimethyl-2-propynylene)-1-piperazinyl, 4-(3,3-dimethyl-1-propynylene)-1-piperazinyl, 4-(3-butynylene)-1-piperazinyl, 4-(1-butynylene)-1-piperazinyl, 4-(2-pentynylene)-1-piperazinyl, 4-(1-pentynylene)-1-piperazinyl, 4-(3-pentynylene)-1-piperazinyl, 4-(4-pentynylene)-1-piperazinyl, 4-(2-hexynylene)-1-piperazinyl, 4-(1-hexynylene)-1-piperazinyl, 4-(3-hexynylene)-1-piperazinyl, 4-(4-hexynylene)-1-piperazinyl, 4-(5-hexynylene)-1-piperazinyl, 4-piperazinyl, 4-(1,3-hexadienylene)-1-piperazinyl, 4-(1,4-hexadienylene)-1-piperazinyl, 4-(1,3,5-hexatrienylene)-1-piperazinyl, 4-(1-propenylene)-1-piperazinylethylene, 4-(1-propenylene)-1-piperazinylpropylene, 4-(1-methyl-1-

- 1 propenylene)-1-piperazinylmethylene, 4-(2-methyl-1-propenylene)-1-piperazinylethylene, 4-(2-propenylene)-1-piperazinylpropylene, 4-(2-butenylene)-1-piperazinylmethylene, 4-(1-butenylene)-1-piperazinylethylene, 4-(2-pentenylene)-1-piperazinylmethylene, 4-(1,3-butadienylenes)-1-piperazinylmethylene, 4-(1,3-pentadienylene)-1-piperazinylmethylene, 4-(1-propynylene)-1-piperazinylmethylene, 4-(2-propynylene)-1-piperazinylethylene, 4-ethylene-1-piperazinylmethylene and 4-(3-butynylene)-1-piperazinylmethylene groups and others can be exemplified.
- 10 piperazinylmethylene groups and others can be exemplified.

As to the tetrazolyl group which may have a lower alkyl group as the substituent, a tetrazolyl group which may have an alkyl group having 1 to 6 carbon atom as the substituent, such as tetrazolyl, 1-

- 15 methyl-5-tetrazolyl, 1-ethyl-5-tetrazolyl, 1-propyl-5-tetrazolyl, 1-tert-butyl-5-tetrazolyl, 1-pentyl-5-tetrazolyl, 1-hexyl-5-tetrazolyl, 5-methyl-1-tetrazolyl, 5-isopropyl-1-tetrazolyl, 5-n-butyl-1-tetrazolyl, and 5-hexyl-1-tetrazolyl groups and others can be exemplified.
- 20 fied.

As to the phenyl group which may have a hydroxyl group as the substituent, phenyl, 2-, 3- or 4-hydroxy-phenyl group can be exemplified.

- As to the straight-chain or branched-chain
- 25 unsaturated hydrocarbon group which may have or may not have an oxygen atom or a group of the formula  $-N^7-R^7$   
(wherein  $R^7$  is a lower alkyl group), a straight-chain or branched-chain unsaturated hydrocarbon residual group

- 1 having 2 to 6 carbon atoms in the unsaturated hydro-carbon residual moiety, having 1 to 3 double bonds and/or triple bonds therein, said unsaturated hydrocarbon residual group may have or may not have an oxygen atom or
- 5 a group of the formula  $\text{-N}-\overset{\text{R}^7}{\underset{|}{\text{R}}}$  (wherein  $\text{R}^7$  is an alkyl group having 1 to 6 carbon atoms), such as vinylene, 1-propenylene, 1-methyl-1-propenylene, 2-methyl-1-propenylene, 2-propenylene, 2-butenylene, 1-butenylene, 3-butenylene, 2-pentenylene, 1-pentenylene, 3-pentenylene,
- 10 4-pentenylene, 1,3-butadienylene, 1,3-pentadienylene, 2-penten-4-ynylene, 2-hexenylene, 1-hexenylene, 5-hexenylene, 3-hexenylene, 4-hexenylene, 3,3-dimethyl-1-propenylene, 2-ethyl-1-propenylene, ethynylene, 2-propynylene, 1-propynylene, 1,1-dimethyl-2-propynylene,
- 15 3,3-dimethyl-1-propynylene, 2-butynylene, 3-butynylene, 1-butynylene, 2-pentynylene, 1-pentynylene, 3-pentynylene, 4-pentynylene, 2-hexynylene, 1-hexynylene, 3-hexynylene, 4-hexynylene, 5-hexynylene, 1,3-hexadienylene, 1,4-hexadienylene, 1,3,5-hexatrienylene, 1-propenyleneoxy,
- 20 1-methyl-1-propenyleneoxy, 2-methyl-1-propenyleneoxy, 2-propenyleneoxy, 2-butenyleneoxy, 1-propenyleneoxy methylene, 1-butenyleneoxy, 3-butenyleneoxy, 2-pentenyleneoxy, 1-pentenyleneoxy, 3-pentenyleneoxy, 4-pentenyleneoxy, 1,3-butadienyleneoxy, 1,3-pentadienyleneoxy,
- 25 2-penten-4-ynyleneoxy, 2-hexenyleneoxy, 1-hexenyleneoxy, 5-hexenyleneoxy, 3-hexenyleneoxy, 4-hexenyleneoxy, 3,3-dimethyl-1-propenyleneoxy, 2-ethyl-1-propenyleneoxy, ethynyleneoxy, 2-propynyleneoxy, 1-propynyleneoxy, 1,1-

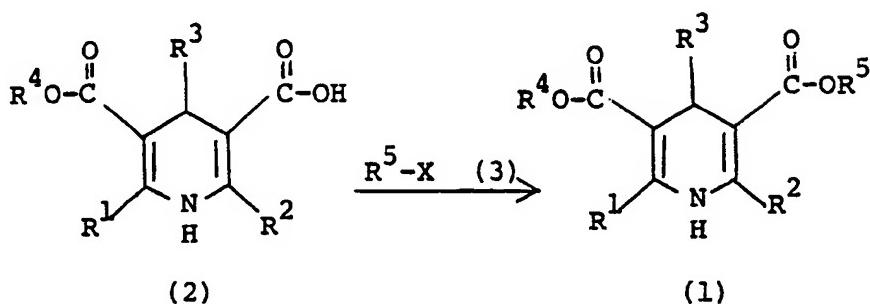
- 1 dimethyl-2-propynyleneoxy, 3,3-dimethyl-1-propynyleneoxy,  
3-butynyleneoxy, 1-butynyleneoxy, 2-pentynyleneoxy, 1-  
pentynyleneoxy, 3-pentynyleneoxy, 4-pentynyleneoxy,  
2-hexynyleneoxy, 1-hexynyleneoxy, 3-hexynyleneoxy, 4-  
hexynyleneoxy, 5-hexynyleneoxy, 1,3-hexadienyleneoxy,  
1,4-hexadienyleneoxy, 1,3,5-hexatrienyleneoxy, 1-  
propyleneoxyethylene, 1-propyleneoxypropylene, 1-  
methyl-1-propyleneoxymethylene, 2-methyl-1-propylene-  
oxyethylene, 2-propyleneoxypropylene, 2-butenyleneoxy-  
methylene, 1-butenyleneoxyethylene, 2-pentenyleneoxy-  
methylene, 1,3-butadienyleneoxymethylene, 1,3-pentadienyl-  
eneoxymethylene, 1-propynyleneoxymethylene, 2-propynyl-  
eneoxyethylene, ethynyleneoxymethylene, 3-butynylene-  
oxymethylene, 1-butynyleneoxyethylene, 1-pentynylene-  
oxymethylene, 3,3-dimethyl-1-propynyleneoxymethylene,  
N-methyl-N-(1-propylene)amino, N-ethyl-N-(1-methyl-1-  
propylene)amino, N-propyl-N-(2-methyl-1-propylene)-  
amino, N-n-butyl-N-(2-propylene)amino, N-pentyl-N-  
(2-butenylene)amino, N-methyl-N-(1-propylene)amino-  
methylene, N-hexyl-N-(1-butenylene)amino, N-methyl-N-  
(3-butenylene)amino, N-ethyl-N-(2-tentenylene)amino,  
N-propyl-N-(1-pentenylene)amino, N-tert-butyl-N-(3-  
pentenylene)amino, N-pentyl-N-(4-pentenylene)amino, N-  
hexyl-N-(1,3-butadienylene)amino, N-methyl-N-(1,3-  
pentadienylene)amino, N-ethyl-N-(2-penten-4-ynylene)-  
amino, N-propyl-N-(2-hexenylene)amino, N-n-butyl-N-  
(1-hexenylene)amino, N-pentyl-N-(5-hexenylene)amino,  
N-hexyl-N-(3-hexenylene)amino, N-methyl-N-(1-propynylene)-

- 1 amino, N-ethyl-N-(1,1-dimethyl-2-propynylene)amino,  
N-propyl-N-(3,3-dimethyl-1-propynylene)amino, N-tert-  
butyl-N-(3-butynylene)amino, N-pentyl-N-(1-butynylene)-  
amino, N-hexyl-N-(2-pentynylene)amino, N-ethyl-N-(3-  
5 pentynylene)amino, N-methyl-N-(1-pentynylene)amino,  
N-propyl-N-(4-pentynylene)amino, N-butyl-N-(2-hexynylene)-  
amino, N-pentyl-N-(1-hexynylene)amino, N-hexyl-N-(3-  
hexynylene)amino, N-methyl-(4-hexynylene)amino, N-ethyl-  
N-(5-hexynylene)amino, N-propyl-N-(1,3-hexadienylene)-  
10 amino, N-tert-butyl-N-(1,4-hexadienylene)amino, N-  
pentyl-N-(1,3,5-hexatrienylene)amino, N-hexyl-N-(1-  
propynylene)aminoethylene, N-methyl-N-(1-propynylene)-  
aminopropylene, N-ethyl-N-(1-methyl-1-propynylene)-  
aminomethylene, N-propyl-N-(2-methyl-1-propynylene)-  
15 aminoethylene, N-butyl-N-(2-propynylene)aminopropylene,  
N-pentyl-N-(2-butenylene)aminomethylene, N-hexyl-N-  
(1-butenylene)aminoethylene, N-methyl-N-(2-pentynylene)-  
aminomethylene, N-ethyl-N-(1,3-butadienylene)aminomethylene,  
N-propyl-N-(1,3-pentadienylene)aminomethylene, N-methyl-  
20 N-(1-propynylene)aminomethylene, N-butyl-N-(2-propynylene)-  
aminoethylene, N-pentyl-N-ethynyleneaminomethylene,  
N-hexyl-N-(3-butynylene)aminomethylene, N-methyl-N-(1-  
butynylene)aminoethylene, N-ethyl-N-(1-pentynylene)-  
aminomethylene and N-methyl-N-(3,3-dimethyl-1-propyny-  
25 lene)aminomethylene groups and others can be exemplified.

Dihydropyridine derivatives and salts thereof  
represented by the general formula (1) according to the  
present invention can be prepared by various methods,

1 for examples the derivatives can be prepared by the  
following Reaction process formula-1.

Reaction process formula-1



(wherein X is a hydroxyl group or a halogen atom; and  
5 R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are the same as defined above).

In the reaction of compound (2) with compound (3), when X is a hydroxyl group, reaction conditions usually employed in esterification reaction can be used. The reaction may be conducted generally in the presence 10 of a catalyst which is usually used in esterification reactions. As to the typical catalysts, there can be exemplified inorganic acids, such as hydrogen chloride, concentrated sulfuric acid, phosphoric acid, poly-phosphoric acids, boron trifluoride and perchloric acid 15 and others; organic acids, such as trifluoroacetic acid, trifluoromethanesulfonic acid, naphthalenesulfonic acids, p-toluenesulfonic acid, benzenesulfonic acid and ethanesulfonic acid and others; and dehydrating agents, such as trifluoromethanesulfonic acid anhydride, thionyl 20 chloride, tetramethylureaoxalyl chloride, acetone

1 dimethyl acetal, dicyclohexylcarbodiimide (DCC), 1-alkyl-2-halogenopyridinium halide or tosylate, N,N-carbonyldiimidazol and others can be exemplified. Additionally, acidic ion-exchange resins can also be  
5 used as the catalysts. The amount of these catalysts is not restricted in the specific range, and they can be used in any amount usually used in common esterification reaction.

The reaction may be carried out in the absence  
10 or presence of a solvent. As to the solvent used in the reaction, any solvent usually used in common esterification reaction may effectively be used.

Specifically, as to the solvents, aromatic hydrocarbons, for example benzene, toluene and xylene; halogenated  
15 hydrocarbons, for example dichloromethane, dichloroethane, chloroform, carbon tetrachloride and others; ethers, for example diethyl ether, tetrahydrofuran, dioxane, ethylene glycol monomethyl ether, pyridine and others, and mixed solvents thereof can be exemplified.

20 In the above-mentioned reaction, the ratio of the amount of compound (3) to the amount of compound (1) can be selected from a wide range, and the former is used in an equimolar quantity to 5 times the molar quantity, preferably, the equimolar quantity to 2 times the molar  
25 quantity to the latter.

In carrying out of the above-mentioned reaction, the yield of the objective product can be increased by removing the water formed in the reaction from the

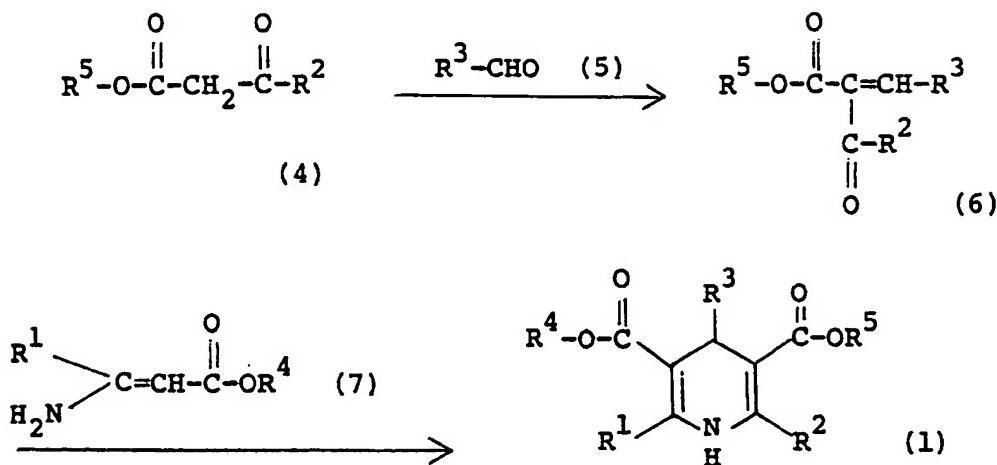
1 reaction system by using a dehydrating agent, such as  
anhydrous calcium chloride, anhydrous copper sulfate,  
anhydrous calcium sulfate, phosphorus pentoxide or the  
like. The reaction temperature of the reaction may be  
5 selected optionally, and there is not any restriction to  
the temperature, generally, the reaction may be carried  
out in the range from about -20° to 200°C, preferably,  
from about 0°C to 150°C. The reaction is completed,  
generally in about 10 minutes to 20 hours depend on  
10 the kind of the starting materials and the reaction  
condition.

In the above-mentioned reaction, when X is a halogen atom, the objective product can be obtained by carrying out the reaction under conditions of dehydrohalogenating reaction. The dehydrohalogenating reaction is carried out by using a basic compound as the dehydrohalogenating agent. As to the basic compound, any known basic compound can be used, for example inorganic basic compounds such as sodium hydroxide, potassium hydroxide,  
15 sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, silver carbonate and others; alcoholates such as sodium methylate, sodium ethylate and others; organic basic compounds such as triethylamine, pyridine, N,N-dimethylaniline  
20 and others can be exemplified.  
25

The dehydrohalogenating reaction can advantageously be carried out in the presence of a solvent, and any inert solvent which does not give any adverse

- 1 effect to the reaction can be used. As to the solvents, alcohols, such as methanol, ethanol, propanol, butanol, ethylene glycol and others; ethers, such as dimethyl ether, tetrahydrofuran, dioxane, ethylene glycol dimethyl
- 5 ether, diethylene glycol dimethyl ether, and others; ketones such as acetone, methyl ether ketone and others; aromatic hydrocarbons, such as benzene, toluene, xylene and others; esters, such as methyl acetate, ethyl acetate and others; aprotic polar solvents, such as
- 10 N,N-dimethylformamide, dimethyl sulfoxide, hexamethyl-phosphoryl triamide and others can be exemplified. Said reaction can also be carried out in the presence of a metal iodide, such as sodium iodide, potassium iodide and others. The ratio of the amount of a compound (3)
- 15 to the amount of a compound (2) is not specifically restricted and can be selected from a wide range, generally an equimolar quantity to 5 times the molar quantity, preferably an equimolar quantity to 2 times the molar quantity of the former is used to the latter.
- 20 The reaction temperature is also not specifically restricted, and generally the reaction is carried out at a room temperature to 200°C, preferably at from a room temperature to 160°C. The reaction is preferably carried out in 1 to 30 hours. Thus, dihydropyridine derivatives
- 25 represented by the general formula (1) can be prepared.

1 Reaction process formula-2



(wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are the same as defined above).

- The reaction of compound (4) with compound (5)
- 5 in the above-mentioned reaction process formula-2 can also be carried out in a suitable solvent in the presence or absence of a catalyst.

As to the solvent, alcohols, such as methanol, ethanol, propanol, isopropanol, butanol, ethylene glycol, 10 and others; ethers, such as tetrahydrofuran, dioxane, ethylene glycol dimethyl ether, diethylene glycol dimethyl ether and others; aromatic hydrocarbons, such as benzene, toluene, xylene and others; halogenated hydrocarbons, such as methylene chloride, chloroform, 15 1,2-dichloromethane, and others; aprotic polar solvents, such as dimethyl sulfoxide, N,N-dimethylformamide, hexamethylphosphoryl triamide and others; carboxylic acids,

- 1 such as acetic acid, propionic acid and others; and  
pyridine can be exemplified.

As to the catalyst used in the reaction, organic basic compounds, such as pyridine, piperidine, triethylamine, 5 diethylamine, 1,8-diazabicyclo[5.4.0]undecene-5 (DBU) and others; metal alcoholates, such as sodium ethylate, sodium methyllyate and others, inorganic basic compounds, such as sodium hydroxide, potassium hydroxide, potassium carnoate, potassium acetate and others; mineral acids, 10 such as hydrochloric acid, sulfuric acid and others; carboxylic acid, such as acetic acid, propionic acid and others, Lewis acids, such as boron trifluoride can be exemplified.

As to the ratio of the amount of compound (4) 15 to the amount of compound (5), the latter may be used in an equimolar quantity, preferably an equimolar quantity to 2 times the molar quantity to the former. As to the amount of the catalyst, 0.01 to 10 times the molar quantity, preferably, 0.1 to 5 times the molar quantity 20 of the catalyst may be used to compound (4). The reaction may be carried out, generally at -20 to 200°C, preferably, -20 to 150°C, and the reaction is completed generally, in 10 minutes to 50 hours.

The reaction of compound (6) with compound (7) 25 can advantageously be carried out in the presence of a solvent. As to the solvent, any inert solvent which does not give any adverse effect to the reaction can be used, for example, ketones, such as acetone; halogenated

1 hydrocarbons such as chloroform and others; alcohols,  
such as methanol, ethanol, propanol, isopropanol, ethylene  
glycol and others; ethers, such as diethyl ether,  
tetrahydrofuran, dioxane, ethylene glycol dimethyl ether,  
5 diethylene glycol dimethyl ether and others; aromatic  
hydrocarbons, such as benzene, toluene, xylene and others;  
esters, such as methyl acetate, ethyl acetate and others;  
carboxylic acid, such as acetic acid, propionic acid  
and others; organic basic compounds such as pyridine and  
10 others; and aprotic polar solvent such as N,N-dimethyl-  
formamide, dimethyl sulfoxide, hexamethylphosphoryl  
triamide and others can be exemplified.

The ratio of the amount of compound (6) to the  
amount of compound (7) may be an equimolar quantity to  
15 10 times the molar quantity, preferably an equimolar  
*of the latter may be used*  
quantity to 2 times the molar quantity to the former.  
The reaction may generally be carried out at -20° to 200°C,  
preferably at 50° to 150°C. The reaction is generally  
completed in 10 minutes to 20 hours, then the desired  
20 compound represented by formula (1) can be obtained

In conducting the reaction of compound (4)  
with compound (5) to form compound (6), then reacting  
compound (6) with compound (7) to prepare the desired  
compound (1), the intermediate compound (6) may not be  
25 separated from the reaction system, thus compound (5)  
and compound (7) may be existed within the same reaction  
system and make them reacted in a simultaneous (in one  
step) reaction.

1 Among the dihydropyridine derivatives represented  
by the general formula (1), those having, as for the  
symbol R<sup>8</sup>, a phenyl group which contains at least one  
hydroxyl group as the substituent may be prepared by  
5 hydrolyzing a compound among those represented by the  
general formula (1) having, as for the symbol R<sup>8</sup>, a  
phenyl group which contains at least one substituent  
selected from the group consisting of a lower alkoxy  
group, a tetrahydropyranyloxy group, a lower alkanoyloxy  
10 group and a lower alkoxy-lower alkoxy group.

The hydrolyzing reaction of the compound (1)  
[hereinafter referred to as "compound (1a)"] having, as  
for the symbol R<sup>8</sup>, a phenyl group which contains at  
least one substituent selected from the group consisting  
15 of a lower alkoxy group, a tetrahydropyranyloxy group and  
a lower alkoxy-lower alkoxy group is carried out without  
in a solvent or with in a suitable solvent, by reacting  
an acid. As to the solvent used in this hydrolyzing  
reaction, water; nitrobenzene; aromatic hydrocarbons such  
20 as benzene, toluene, xylene and others; saturated,  
hydrocarbons such as hexane, octane and others; lower  
alcohols such as methanol, ethanol, isopropanol and  
others; ethers such as dioxane, tetrahydrofuran and  
others; ketones such as acetone and others; acetic acid;  
25 acetonitrile and mixed solvents thereof can be exemplified.  
As to the acid used in this hydrolyzing reaction, mineral  
acids such as hydrochloric acid, hydrobromic acid, sulfuric  
acid and others; p-toluenesulfonic acid; pyridine

1 p-toluenesulfonate; carboxylic acids such as acetic  
acid, propionic acid and others; aluminium chloride; tin  
chloride; boron trifluoride; zinc chloride and others  
can be exemplified. The amount of the acid to be  
5 used to the amount of compound (1a) may be at least an  
equimolar quantity, generally a large excess quantity  
may be used. The reaction may be carried out generally  
from -30° to 200°C, preferably from -30° to 100°C, and  
the reaction is generally completed in about 0.5 to 8  
10 hours.

The hydrolyzing reaction of the compound (1)  
having, as for the symbol R<sup>8</sup>, a phenyl group which  
contains at least one lower alkanoyloxy group, is carried  
out under reaction conditions widely employed in hydro-  
lyzing reaction of esters. For example, the hydrolyzing  
reaction is carried out under conditions of in the  
presence of an acid or alkali catalyst, in an inert  
solvent at 0° to 100°C, for 1 to 5 hours. As to the  
catalyst, inorganic acids such as hydrochloric acid,  
15 sulfuric acid, aluminium chloride and others; organic  
acids such as acetic acid, formic acid and others;  
inorganic basic compounds such as sodium hydroxide  
sodium carbonate, potassium hydroxide and others;  
ammonia; organic basic compounds such as triethylamine  
20 and others can be exemplified. As to the inert solvent,  
water; alcohols such as methyl alcohol, ethyl alcohol  
and others; carboxylic acids such as acetic acid, propionic  
acid and others; ethers such as diethyl ether and others;

- 1 amides such as dimethylformamide, acetamide and others can be exemplified.

Among the dihydropyridine derivatives represented by the general formula (1), those having, as for 5 the symbol R<sup>8</sup>, a phenyl group which contains at least one substituent selected from the group consisting of a lower alkoxy group, a tetrahydropyranylloxy group and a lower alkoxy-lower alkoxyl group, can also be prepared by alkylating a compound hereinafter referred to as 10 "compound (1b)" having, as for the symbol R<sup>8</sup>, a phenyl group which contains at least one hydroxyl group as the substituent. Said alkylating reaction is carried out under conditions usually employed in common alkylating reaction. For example, alkylation is carried out by 15 using an alkylating agent in the presence of a basic compound. As to the basic compound used in this reaction, alkali metals such as metallic sodium, metallic potassium and others; and the hydrides, hydroxides, carbonates, bicarbonates or alcoholates of these alkali metals;

20 aromatic amines compounds such as pyridine, piperidine, and others; organic basic compounds such as triethylamine, N,N-diethylaniline, 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) and others can be exemplified. As to the alkylating agent, a lower alkyl halide, a tetrahydropyranyl halide, 25 dihydropyran, a lower alkoxy-lower alkyl halide, a dialkyl sulfate, a diazoalkane and others can be exemplified.

In using a lower alkyl halide, a tetrahydro-

- 1 pyranyl halide or a lower alkoxy-lower alkoxy halide as the for alkylating agent, the alkylating reaction is carried out effectively in a suitable solvent. As to the solvent to be used, water; a lower alcohols such as
- 5 methanol, ethanol, isopropanol, n-butanol and others; ethers such as diethyl ether, dioxane, tetrahydrofuran and others; ketones such as acetone, methyl ethyl ketone and others; halogenated hydrocarbons such as chloroform, dichloroethane and others; aromatic hydrocarbons such as
- 10 nitrobenzene, chlorobenzene, benzene, toluene, xylene and others; aprotic polar solvents such as N,N-dimethyl-formamide, dimethyl sulfoxide and others can be exemplified. The amount of the alkylating agent to the amount of compound (1b), at least an equimolar quantity,
- 15 preferably an equimolar quantity to 5 times the molar quantity may be used to the latter. The reaction is generally carried out at from -20° to 200°C, preferably at 0° to 100°C, and is completed in about 10 minutes to 24 hours.
- 20 In using a dialkyl sulfate as for the alkylating agent, the alkylation reaction is carried out in an inert solvent at a room temperature to 150°C. As to the dialkyl sulfate, dimethyl sulfate, diethyl sulfate and others can be exemplified. As to the inert solvent,
- 25 aromatic hydrocarbons such as benzene, toluene and others; ethers such as dioxane, tetrahydrofuran, diethyl ether and others can be exemplified.

In using dihydropyran as for the alkylating

1 agent, the alkylating reaction is carried out in the presence of an acid, in a solvent, and generally at 0° to 150°C, preferably at 0° to about 100°C, and the reaction is completed in 0.5 to 10 hours. As to the acid 5 to be used in this case, mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and others; p-toluenesulfonic acid; pyridine p-toluenesulfonate and others can be exemplified. As to the solvent, lower alcohols such as methanol, ethanol, isopropanol and 10 others; ethers such as diethyl ether, dioxane, tetrahydrofuran and others; aromatic hydrocarbons such as benzene, toluene and others; saturated hydrocarbons such as hexane, octane and others; ketones such as acetone and; acetic acid; acetonitrile and mixtures of 15 these solvents can be exemplified.

The amount of dihydropyran to the amount of compound (lb), generally an equimolar quantity, preferably an equimolar to 5 times the molar quantity of the former may be used to the latter.

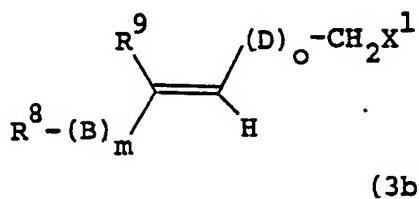
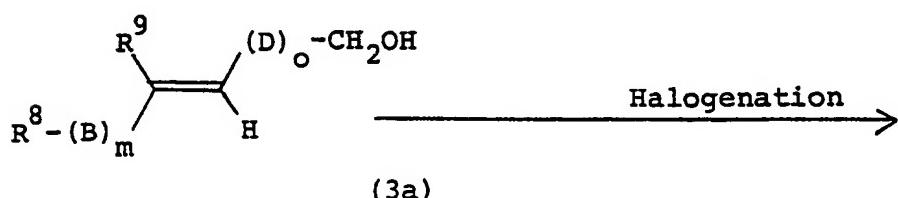
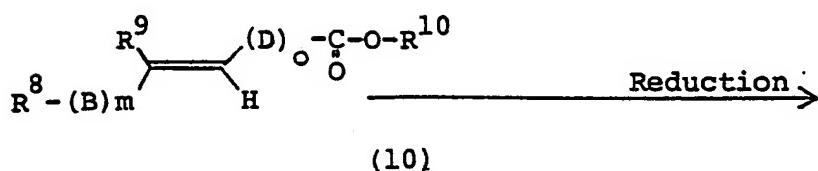
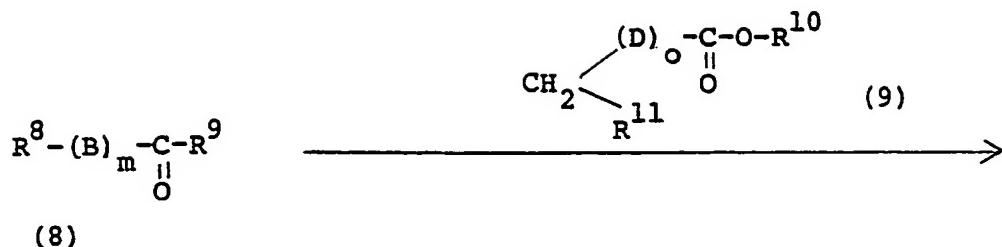
20 Among the dihydropyridine derivatives represented by the general formula (1), those having, as for the symbol R<sup>8</sup>, a phenyl group which contains at least one lower alkanoyloxy group as the substituent, can also be prepared by acylating a compound (lb). 25 Said acylating reaction is carried out by using an acid halide such as a lower alkanoic acid halide, or an alkanoic acid anhydride under conventional method. The reaction by using acid halide is carried out in an inert

1 solvent, and if necessary in the presence of a dehydro-  
halogenating agent such as an amine for example tri-  
ethylamine, diisopropylethylamine, pyridine, N,N-  
diethylaniline and others, and at -50° to 150°C, in 1  
5 to 24 hours. In carrying out the acylating reaction  
by using acid anhydride, the reaction is conducted in  
an inert solvent at a room temperature to 200°C, in 1  
to 10 hours. As to the inert solvent used in the above-  
mentioned reaction, aromatic hydrocarbons such as  
10 nitrobenzene, chlorobenzene and others; amines such as  
pyridine, N,N-dimethylaniline and others; ethers such  
as ~~diethyl~~ ether, tetrahydrofuran and others; halogenated  
hydrocarbons such as dichloromethane, dichloroethane,  
chloroform and others can be exemplified. The amount of  
15 the acylating agent used to the amount of compound (1b),  
generally at least an equimolar quantity, preferably an  
equimolar to 5 times the molar quantity of the former may  
be used to the latter.

Compounds represented by the general formula

20 (3) as used for the starting material in the above-  
mentioned reaction process formula-1, and compounds  
represented by the general formula (4) as used for the  
starting material in the above-mentioned reaction process  
formula-2 contain novel compounds, said compounds  
25 represented by the general formulas (3a), (3b), (3c) and  
(3d) are prepared by the following reaction process  
formulas-3 to -5.

## 1 Reaction process formula-3



[wherein R<sup>8</sup> is the same as defined above; R<sup>9</sup> is a hydrogen atom or a lower alkyl group; R<sup>10</sup> is a lower alkyl group; R<sup>11</sup> is a carboxyl group or a group of the formula  $\text{-P}(\text{OR}^{10'})_2\text{O}$

5 (wherein R<sup>10</sup> is a lower alkyl group); B and D are each an unsaturated alkylene group; m and o are 0 or 1 respectively; X<sup>1</sup> is a halogen atom; provided that the carbon

1 atom number in the group of the formula  $\text{CH}_2\begin{array}{c} \diagup \\ \text{(D)} \end{array}\text{O}^-$  - should  
not exceed 6].

The reaction of compound (8) with compound (9) can be carried out in the presence of a basic compound, 5 in a solvent. As to the basic compound, inorganic basis such as metallic sodium, metallic potassium, sodium hydride, sodium amide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate and others; metal alcoholates such 10 as sodium methylate, sodium ethylate and others; organic basis compounds such as pyridine, piperidine, quinoline, triethylamine, N,N-dimethylaniline and others can be exemplified. As to the solvent, any inert solvent which does not give any adverse effect to the reaction can be 15 used, for example, ethers such as diethyl ether, dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, diethylene glycol dimethyl ether and others; aromatic hydrocarbons such as benzene, toluene, xylene and others; aliphatic hydrocarbons n-hexane, heptane, cyclohexane 20 and others, amines such as pyridine, N,N-dimethylaniline and others; aprotic polar solvents such as N,N-dimethyl-formamide (DMF), dimethyl sulfoxide (DMSO), hexamethyl-phosphoryl triamide (HMPA) and others can be exemplified. The reaction is generally carried out at 0° to 150°C, 25 preferably from a room temperature to about 120°C, and is generally completed in 0.5 to 15 hours. The amount of compound (8) to the amount of compound (9) is generally

- 1 an equimolar quantity, preferably an equimolar quantity to 2 times the molar quantity of the latter is used to the former.

The reduction of compound (10) is generally

- 5 carried out by using a hydrogenation reducing agent. As to the hydrogenation reducing agent, sodium borohydride, lithium aluminum hydride, aluminum dialkyl hydride such as aluminum diisobutyl hydride (DIBAL), diborane and others. The amount of the hydrogenation reducing agent
- 10 to the amount of compound (10) is that generally 0.1 to 3 times the molar quantity, preferably 0.5 to 2 times the molar quantity of the former is used to the latter. The reaction is carried out generally in a suitable solvent, for example water; a lower alcohols such as methanol,
- 15 ethanol, isopropanol and others; ethers such as tetrahydrofran, diethyl ether, diethylene glycol dimethyl ether and others; aromatic hydrocarbons such as benzene, toluene, xylene and others can be used, at -60° to 50°C, preferably at -40°C to a room temperature, for about 10
- 20 minutes to 5 hours. In carrying out of the reaction by using lithium aluminum hydride, aluminum dialkyl hydride or diborane as for the reducing agent, an anhydrous solvent such as diethyl ether, tetrahydrofuran, diethylene glycol dimethyl ether, benzene, toluene or
- 25 xylene may preferably be used.

The halogenation reaction of compound (3a) thus prepared is carried out in a solvent for example, an ether such as dioxane, tetrahydrofuran or the like; a

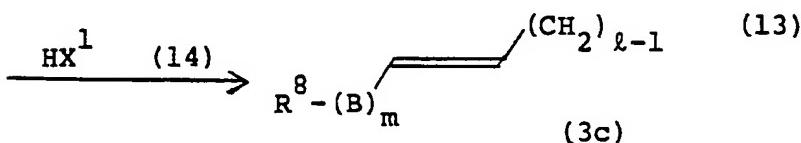
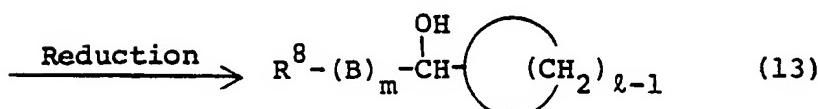
1 chlorinated hydrocarbon such as chloroform, methylene chloride, carbon tetrachloride or the like, or without a solvent, by reacting a compound (3a) with a halogenating agent for example a hydrohalic acid such as hydrochloric acid or hydrobromic acid; N,N-diethyl-1,2,2-trichlorovinylamide, phosphorus pentachloride, phosphorus pentabromide, phosphorus oxychloride, thionyl chloride or the like, at a room temperature to 150°C, preferably at a room temperature to 80°C, for 1 to 6 hours. The amount of the halogenating agent to the amount of a compound (3a) is that at least an equimolar quantity, generally a large excess quantity of the halogenating agent may be used to the latter.

Reaction process formula-4



(11)

(12)



15 [wherein  $R^8$ ,  $B$ ,  $m$  and  $X^1$  are the same as defined above;

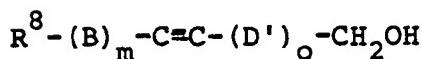
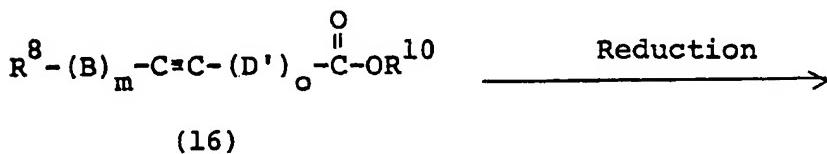
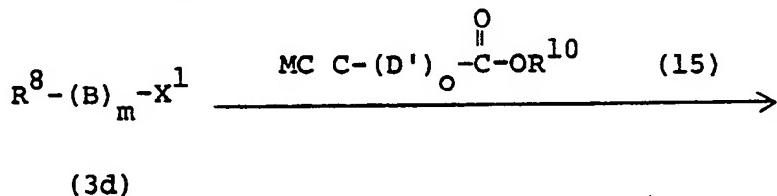
1 l is an integer of 3 to 6; provided that the number of carbon atoms in a group of the formula -(B)<sub>m</sub>-CH=CH-(CH<sub>2</sub>)<sub>l-1</sub> should not be over 6].

The reaction for preparing compound (12) from compound (11) is carried out in the presence of a basic compound, in an inert solvent for example, an ether such as dioxane, tetrahydrofuran, ethylene glycol dimethyl ether or the like; an aromatic hydrocarbon such as benzene, toluene, xylene or the like; a lower alcohol such as methanol, ethanol, isopropanol or the like; a polar solvent such as acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide or the like. As to the basic compound, inorganic basic compounds such as calcium carbonate, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, sodium hydroxide, potassium hydroxide, sodium amide, sodium hydride, potassium hydride, sodium methylate, sodium ethylate and others; and organic basic compounds such as triethylamine, pyridine, quinoline, 1,5-diazabicyclo[4,3,0]nonene-5 (DBN), 1,8-diazabicyclo-[5,4,0]undecene-7 (DBU), 1,4-diazabicyclo[2,2,2]octane (DABCO) and others can be exemplified. The reaction is generally carried out at a room temperature to 200°C, preferably at 60° to 120°C, and the reaction is generally completed in 1 to 24 hours.

25 Reduction reaction of a compound (12) is carried out under the same conditions similar to those employed in the reduction of a compound (10) in the above-mentioned reaction process formula-3.

- 1        The reaction of a compound (13) with a compound (14) is carried out in a suitable inert solvent. As to the solvent to be used in the reaction, ethers such as dioxane, tetrahydrofuran, diethyl ether and others; 5 halogenated hydrocarbons such as chloroform, methylene chloride, carbon tetrachloride and others can be exemplified. The reaction temperature is generally at 0 to 150°C, preferably at 0° to about 100°C, and generally, the reaction is completed in 10 minutes to 6 hours.
- 10      The amount of the compound (14) to the amount of the compound (13) is that generally at least an equimolar quantity, preferably in a large excess amount of the former is used to the latter.

Reaction process formula-5



(3e)

15 [wherein  $\text{R}^8$ ,  $\text{R}^{10}$ ,  $\underline{\text{B}}$ ,  $\text{X}^1$ ,  $\underline{\text{m}}$  and  $\underline{\text{o}}$  are the same as defined

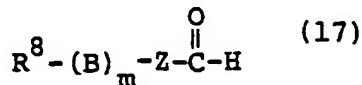
1 above; M is a metal such as copper, sodium, lithium,  
potassium; D' is a saturated- or unsaturated-alkylene  
group; provided that the number of the carbon atoms in  
a group of the formula  $-(B)_m-C\equiv C-(D')_n$  should not be  
5 exceed over 6].

The reaction of a compound (3d) with a compound  
(15) is carried out in a suitable solvent. As to the  
solvent used in the reaction, ethers such as diethyl  
ether, dioxane, tetrahydrofuran, ethylene glycol dimethyl  
10 ether, diethylene glycol dimethyl ether and others;  
aromatic hydrocarbon such as benzene, toluene, xylene;  
aliphatic hydrocarbons such as n-hexane, heptane, cyclo-  
hexane and others; amines such as triethylamine, pyridine,  
N,N-dimethylaniline and others; aprotic polar solvents  
15 such as N,N-dimethylformamide (DMF), dimethyl sulfoxide  
(DMSO), hexamethylphosphoryl triamide (HMPA) and others  
can be exemplified. The reaction temperature is generally  
0° to 200°C, preferably from a room temperature to at  
about 150°C, and the reaction is generally completed in  
20 0.5 to 10 hours. The amount of the compound (15) to  
the amount of the compound (3d) is that at least an  
equimolar quantity, preferably an equimolar to 1.5 times  
the molar quantity of the former is used to the latter.

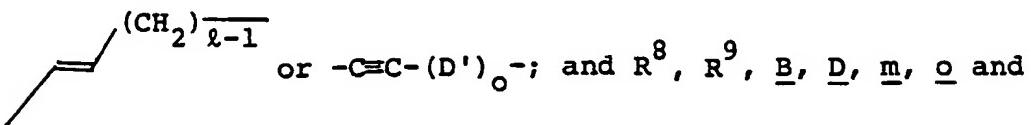
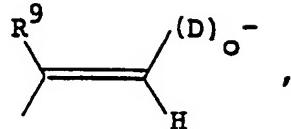
The reduction reaction of a compound (16) can  
25 be carried out under the same conditions those employed  
in the reduction of a compound (10) in reaction process  
formula-3.

Compounds represented by the general formulas

1 (3a), (3b), (3c) and (3d) can be converted into a compound represented by the general formula (17),



[wherein Z is a group of the formula



5  $\underline{l}$  are the same as defined above],  
by oxidizing in the presence of a suitable oxidizing agent.

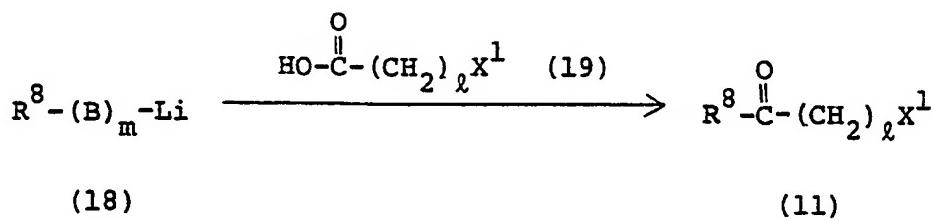
A part of compounds represented by the general formula (17) correspond to compound (8) which is the starting material used in the above-mentioned reaction

10 process formula-3, thus various desired compounds represented by the general formula (3) can be obtained by carrying out the reaction in sequence in the above-mentioned reaction process formulas-3 to -5 and -9 and the above-mentioned oxidation reaction. As to the oxidizing  
15 agent used in the above-mentioned oxidation reaction, chromium compounds such as potassium chromate, sodium bichromate, chromium trioxide, pyridinium chlorochromate, anhydrous chromium trioxide-dipyridine complex and others; manganese compounds such as manganese dioxide, potassium permanganate and others; lead tetraacetate; periodic acid; dimethyl sulfoxide; amine oxides such as dimethylamine oxide; pyridine-nitroso compounds such as pyridine-p-

- 1 nitro-N,N-dimethylaniline and others can be exemplified. As to the solvent used to the reaction, aromatic hydrocarbons such as benzene, toluene, xylene and others; halogenated hydrocarbons such as methylene chloride,
- 5 chloroform, carbon tetrachloride and others; ethers such as diethyl ether, dioxane, tetrahydrofuran and others, aliphatic hydrocarbons such as hexane, pentane, cyclohexane and others, ketones such as acetone, methyl ethyl keton and others; lower alcohols such as methanol,
- 10 ethanol, isopropanol; water, acetic acid, dimethyl sulfoxide and others can be exemplified. The reaction can be carried out by using an acid such as sulfuric acid or perchloric acid as the catalyst. The reaction is carried out generally at 0° to 200°C, preferably at 0°
- 15 to about 150°C, is completed generally in 0.5 to 15 hours.

A compound represented by the general formula (11) as used for the starting material in the above-mentioned reaction is prepared by for example the following reaction process formula-7.

20 Reaction process formula-7



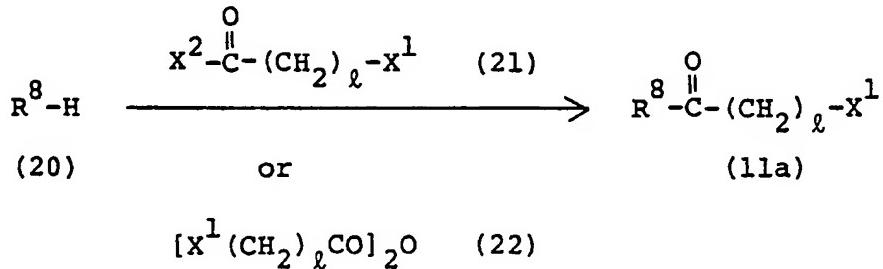
[wherein  $R^8$ ,  $B$ ,  $m$ ,  $l$  and  $X^1$  are the same as defined above].

1       The reaction of a compound (18) with a compound  
5       (19) is carried out in a suitable solvent. As to the  
10      solvent used in the reaction, ethers such as diethyl  
15      ether, dioxane, tetrahydrofuran, 1,2-dimethoxyethane  
20      and others; aromatic hydrocarbons such as benzene,  
25      toluene, xylene and others; aliphatic hydrocarbons such  
30      as hexane, heptane, pentane and others; and mixtures of  
35      these solvents and others can be exemplified.

40      The reaction is carried out generally at -70° to  
45      50°C, preferably -65°C to about a room temperature,  
50      and is generally completed in 3 to 30 hours. The amount  
55      of the compound (19) to the amount of the compound (18)  
60      is that at least 2 times the molar quantity, preferably  
65      2 to 3 times the molar quantity of the former is used to  
70      the latter.

75      Among the compounds represented by the general  
80      formula (11), those in which the symbol m is 0 thus  
85      compound (11a) may be prepared by the following reaction  
90      process formula-8.

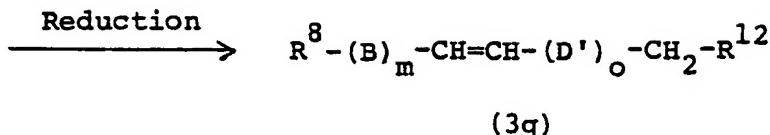
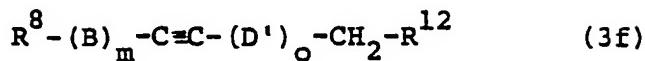
95      20 Reaction process formula-8



- 1 (wherein R<sup>8</sup>, X<sup>1</sup> and l are the same as defined above; and X<sup>2</sup> is a halogen atom).

The reaction of a compound (20) with a compound (21) or compound (22) is generally called as Friedel-Crafts reaction, and can be carried out in a suitable solvent in the presence of a Lewis acid. As to the solvent used in the reaction, any solvent generally used in this type of reaction can advantageously be employed, for example carbon disulfide, nitrobenzene, chlorobenzene, dichloroethane, dichloromethane, trichloroethane, tetrachloroethane and others can be exemplified. As to the Lewis acid used in this reaction, those used conventionally in this type of reaction can preferably be used, for example aluminum chloride, zinc chloride, iron chloride, tin chloride, boron trifluoride, boron tribromide, concentrated sulfuric acid and others can be used. The amount of Lewis acid may be determined suitably, and generally 2 to 6 times the molar quantity, preferably 3 to 4 times the molar quantity of a Lewis acid may be used to a compound (20). The amount of the compound (21) or compound (22) to the amount of the compound (20) is that generally at least an equimolar quantity, preferably an equimolar quantity to 3 times the molar quantity of the former is used to the latter. The reaction temperature can be selected from a wide range, and generally the reaction is carried out at 0° to 120°C, preferably from 0° to 70°C, and the reaction is completed in 0.5 to about 6 hours.

1 Reaction process formula-9



[wherein  $R^8$ ,  $B$ ,  $D'$ ,  $m$  and  $o$  are the same as defined above;  $R^{12}$  is a hydroxyl group or a lower alkanoyl group; provided that the number of the carbon atoms in a group 5 of the formula  $-(B)_m - C \equiv C - (D')_o - CH_2 -$  and a group of the formula  $-(B)_m - CH=CH - (D')_o - CH_2 -$  should not exceed over 6.]

The reduction of a compound (3f) can be carried out by methods according to various reducing reactions known in the art. For example, catalytic reducing 10 method by using palladium black, palladium carbon, platinum oxide, platinum black, Raney nickel, Lindlar catalyst and others as for the reducing catalysts; reducing methods by using sodium borohydride, lithium aluminum hydride and others as for the reducing agents can be employed.

15 In carrying out the catalytic reduction, the reaction can be conducted by using a conventional solvent for example water, methanol, ethanol, isopropanol, acetic acid, dioxane, tetrahydrofuran and others, and in the presence of the above-mentioned catalyst, under a 20 normal atmospheric pressure to 20 atmospheric pressure, preferably, from a normal atmospheric pressure to 10

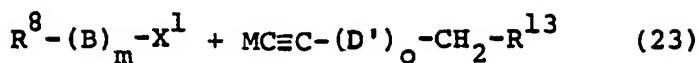
1 atmospheric pressure of hydrogen, and generally at -30°C  
to 100°C, preferably 0°C to 50°C. The amount of the  
catalyst is generally 0.1 to 40% by weight, preferably  
from 1 to 20% by weight of the catalyst is used to a  
5 compound (3f), and the reaction is generally completed  
in 1 to 12 hours.

In carrying out the reaction by using a reducing  
agent such as lithium aluminum hydride, an equimolar  
quantity to 20 times the molar quantity, preferably 1.5  
10 to 3.5 times the molar quantity of the reducing agent is  
used to the compound (2f). The reduction reaction is  
carried out in a conventional solvent such as diethyl  
ether, tetrahydrofuran, dioxane or the like, and generally  
at -30° to 100°C, preferably at 0°C to 70°C, and is  
15 completed in 30 minutes to about 12 hours. According to  
these procedures, a compound represented by the general  
formula (3g) can easily be obtained.

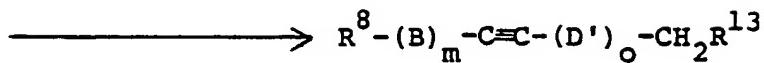
Among the compounds represented by the general  
formula (3g), those having a lower alkanoyloxy group as  
20 for the symbol R<sup>12</sup>, can be converted into a compound (3g)  
having a hydroxy group as for the symbol R<sup>12</sup> under the  
conditions similar to those employed in the hydrolysis  
of a compound (1) wherein R<sup>8</sup> is a phenyl group which  
contains at least one lower alkanoyloxy group as the  
25 substituent.

A part of compounds represented by the general  
formula (3f) can be prepared by a method according to the  
following reaction process formula-10.

1 Reaction process formula-10



(3d)



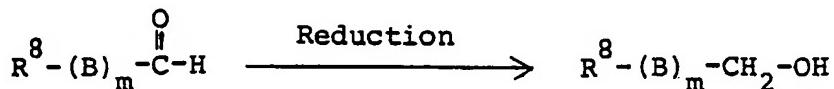
(3h)

[wherein  $R^8$ ,  $B$ ,  $\underline{m}$ ,  $X^1$ ,  $M$ ,  $D'$  and  $o$  are the same as defined above;  $R^{13}$  is a hydroxyl group, tetrahydropyranloxy group, a lower alkoxy-lower alkoxy group or a lower

5 alkanoyl group; provided that the number of the carbon atoms in a group of the formula  $-(B)_{\underline{m}}-C\equiv C-(D')_o-CH_2-$  should not exceed over 6].

The reaction of a compound (3d) with a compound (23) can be carried out under the same reaction  
10 conditions employed in the reaction of a compound (3d) with a compound (15) in the above-mentioned reaction process formula-5.

Reaction process formula-11



(8a)

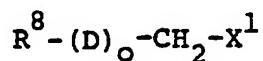
(3h)

[wherein  $R^8$ ,  $B$ , and  $\underline{m}$  are the same as defined above].

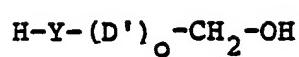
The reduction reaction of a compound (8a) can

- 1 be carried out under the same reaction conditions employed in the reduction of a compound (10) in the above-mentioned reaction process formula-3.

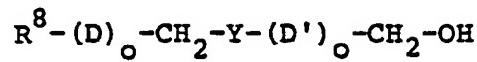
Reaction process formula-12



(24)



(25)



(3i)

- 5 [wherein  $R^8$ , D, D' and  $\underline{o}$  are the same as defined above; Y is an oxygen atom, a sulfur atom, a group of the formula  $-N(\text{cyclohexyl})_2-$  or a group of the formula  $-N(R^7)-R^7$  (wherein  $R^7$  is the same as defined above); provided that the number of the carbon atoms in a group of the formula  $-(D)_o-CH_2-Y-(D')_o-CH_2-$  should not be exceeded over 6].

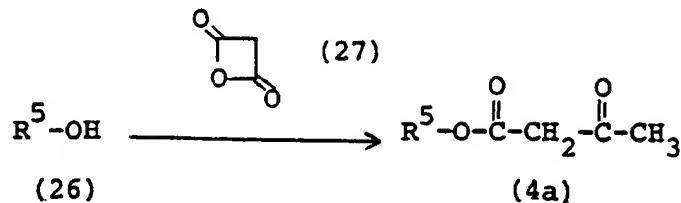
- The reaction of a compound (24) with a compound (25) can be carried out in a suitable solvent or without solvent, in the absence or presence of a basic compound. As to the solvent used in the reaction, water; lower alcohols such as methanol, ethanol, isopropanol and others; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and others; ethers such as diethyl ether, tetrahydrofuran, dioxane and others; aliphatic hydrocarbons such as n-

1 hexane, octane, cyclohexane and others; aromatic hydrocarbons such as benzene, toluene, xylene and others; aprotic polar solvents such as acetone, acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide, hexamethyl-  
5 phosphoryl triamide and others; and mixtures of these solvents can be exemplified. As to the solvent used in the reaction, inorganic basic compounds such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium  
10 hydrogen carbonate, sodium amide, sodium hydride and others; alcoholates such as sodium methylate, sodium ethylate and others; organic basic compounds such as triethylamine, pyridine, N,N-dimethylaniline and others can be exemplified.

15 The said reaction can be advantageously proceeded by using a charge-transfer catalyst such as tetrabutyl-ammonium bromide and others. The reaction is carried out generally, at 0° to 150°C, preferably at 0° to 120°C, and is completed in about 1 to 10 hours. The ratio of  
20 the amount of a compound (24) to the amount of a compound (25) is that generally an equimolar quantity, preferably an equimolar quantity to 10 times the molar quantity of the former is used to the latter.

A compound (4) used as the starting material  
25 in the reaction process formula-2 can be prepared by methods according to reaction process formula-13 and -14 as follows.

1 Reaction process formula-13

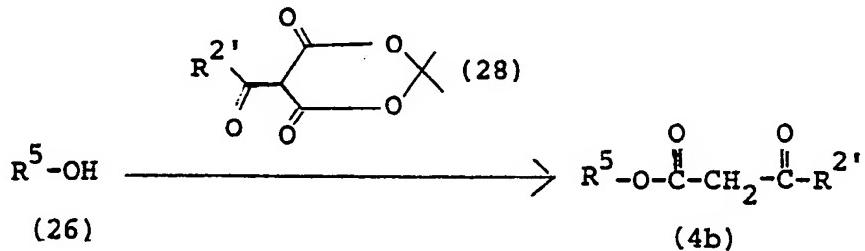


[wherein R<sup>5</sup> is the same as defined above].

The reaction of a compound (26) with a compound (27) in the above-mentioned reaction process formula-13  
5 is carried out in a suitable solvent in the presence of  
a catalyst. As to the catalyst, basic compounds for  
example, organic basic compounds such as triethylamine,  
pyridine, N,N-dimethylaniline and others; inorganic  
basic compounds such as sodium acetate, potassium  
10 carbonate; and acidic compounds for example, sulfonic  
acids such as p-toluenesulfonic acid and others; Lewis  
acids such as boron trifluoride and others can be  
exemplified. As to the solvents, aromatic hydrocarbons  
such as benzene, toluene, xylene and others; esters  
15 such as methyl acetate, ethyl acetate and others; halogen-  
ated hydrocarbons such as methylene chloride, chloroform,  
1,2-dichloroethane and others; ethers such as diethyl  
ether, tetrahydrofuran, dioxane, ethylene glycol  
dimethyl ether, dithylene glycol dimethyl ether and  
20 others; ketones such as acetone, methyl ethyle ketone  
and others; aprotic polar solvents such as N,N-methyl-  
formamide, dimethyl sulfoxide, hexamethylphosphoryl  
triamide, N-methylpyrrolidone and others can be exemplified.

- 1 As to the ratio of the amount of the compound (26) to the amount of the compound (27), generally at least an equimolar quantity, preferably an equimolar quantity to 2 times the molar quantity of the latter may be used to 5 the former. The amount of the catalyst is not specifically restricted, and generally 0.01 to 10 times the molar quantity, preferably 0.1 to 5 times the molar quantity of the catalyst may be used to the compound (26). The reaction is carried out generally at -20° to 200°C, 10 preferably at -20° to 100°C, and is completed in 10 minutes to 20 hours.

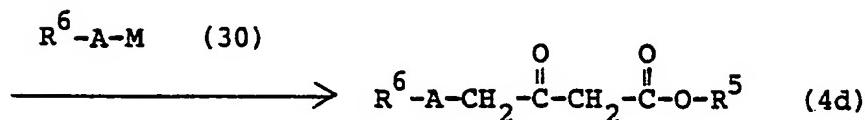
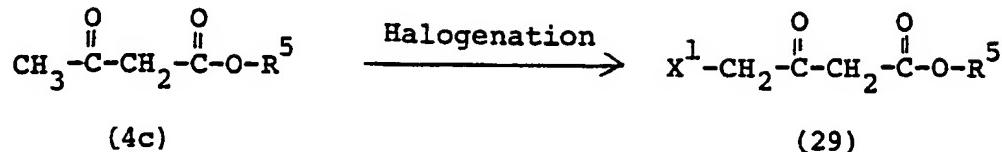
Reaction process formula-14



[wherein  $\text{R}^5$  is the same as defined above; and  $\text{R}^{2'}$  is a lower alkyl group].

- 15 The reaction of a compound (26) with a known compound (28) may be carried out under the same conditions employed in the reaction of a compound (26) with a compound (27) in the above-mentioned reaction process formula-13.

## 1 Reaction process formula-15



[wherein  $R^5$ ,  $x^1$ ,  $M$ , A and  $R^6$  are the same as defined above].

### The halogenation reaction of a compound (4c)

- 5 can be carried out in a suitable solvent, in the presence  
of a halogenating agent. As to the solvent used in the  
halogenation reaction, halogenated hydrocarbons such as  
chloroform, dichloromethane, carbon tetrachloride and  
others; ethers such as diethyl ether, tetrahydrofuran,  
10 dioxane and others; and acetic acid can be exemplified.  
As to the halogenating agent used in this halogenation  
reaction, halogen molecules such as bromine, chlorine and  
others; metal halides such as cupric bromide, cupric  
chloride, lithium chloride and others; thionyl chloride;  
15 N-halogenated succinimides such as N-chlorosuccinimide,  
N-bromosuccinimide and others can be exemplified.

The halogenating agent may generally be used in a large excess amount. The halogenation is carried out generally at 0° to 150°C, preferably at 0° to 120°C,  
20 and is completed in 1 to 24 hours.

The reaction of a compound (29) with a compound

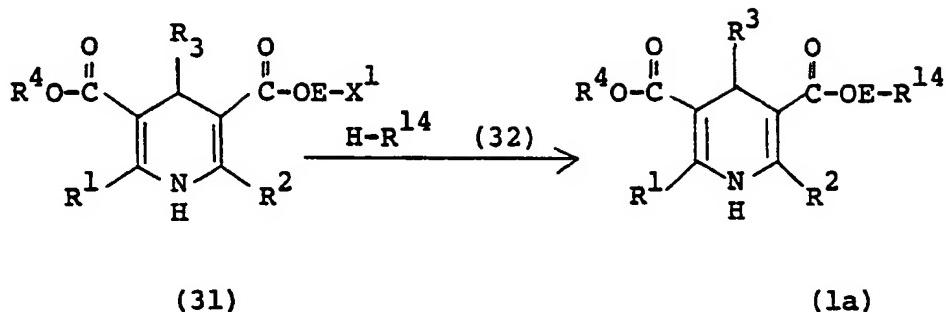
1 (30) can be carried out in a suitable solvent, in the presence of a basic compound. As to the solvent used in this reaction, ethers such as diethyl ether, dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, diethylene  
5 glycol dimethyl ether and others; aromatic hydrocarbons such as benzene, toluene, xylene and others; aliphatic hydrocarbons such as n-hexane, heptane, cyclohexane and others; aprotic polar solvents such as N,N-dimethyl-formamide, dimethyl sulfoxide, hexamethylphosphoryl  
10 triamide and others can be exemplified. As to the basic compounds, inorganic basic compounds such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, metallic sodium, metallic potassium, sodium  
15 amide, sodium hydride and others; alcoholates such as sodium methylate, sodium ethylate and otherss; organic basic compounds such as triethylamine, pyridine, N,N-dimethylaniline and others can be exemplified.

The reaction is generally carried out at a room  
20 temperature to 200°C, preferably at a room temperature to 150°C, and is completed in 1 to 24 hours. The ratio of the amount of the compound (30) to the amount of the compound (29) is generally at least an equimolar quantity, preferably an equimolar quantity to 2 times the molar  
25 quantity of the former is used to the latter.

Dihydropyridine derivatives represented by the general formula (1) can also be prepared by the methods as shown in the following reaction process formula-16

1 and -18.

## Reaction process formula-16



[wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $x^1$  are the same as defined above; E is a lower alkylene group;  $R^{14}$  is a 1,2,3,6-

5 tetrahydropyridyl group which may have, as the substituent, a phenyl group which may have halogen atoms or lower alkyl groups as the substituents on the phenyl ring, group of the formula  $R^6-(D')_o-Y-$  (wherein  $R^6$ ,  $D'$ ,  $Y$  and  $o$  are the same as defined above)].

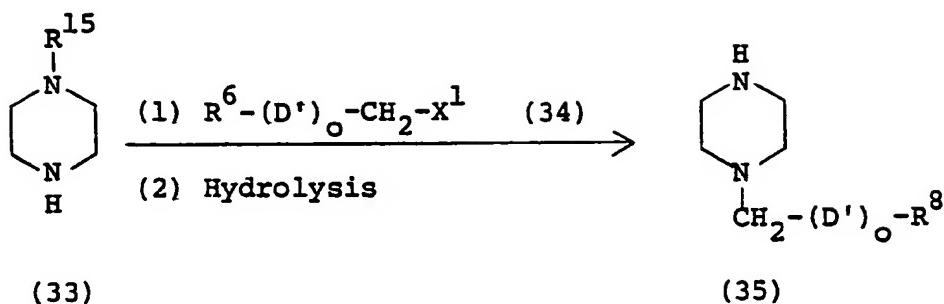
10 The reaction of a compound (31) with a compound  
(32) may be carried out in a suitable solvent, in the  
absence or presence of a basic compound. As to the  
solvent used in the reaction, halogenated hydrocarbons  
such as dichloromethane, dichloroethane, chloroform,  
15 carbon tetrachloride, and others; ethers such as diethyl  
ether, tetrahydrofuran, dioxane, ethylene glycol dimethyl  
ether and others; aliphatic hydrocarbons such as n-hexane,  
octane, cyclohexane and others; aromatic hydrocarbons  
such as benzene, toluene, xylene and others; aprotic polar

1 solvents such as acetone, acetonitrile, N,N-dimethyl-formamide, dimethyl sulfoxide, hexamethylphosphoryl triamide and others can be exemplified. As to the basic compounds used in the reaction, inorganic basic compounds  
5 such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, sodium hydride and others; amines such as triethylamine, diisopropylethylamine, pyridine, quinoline and others can be exemplified. Further, the reaction can be carried  
10 out, if necessary, by adding an alkali metal iodide such as potassium iodide, sodium iodide or the like, or hexamethylphosphoryl triamide as the reaction accelerator. The reaction is carried out at a room temperature to 200°C, preferably at a room temperature to 120°C, and is  
15 completed in 1 to 24 hours.

The ratio of the amount of the compound (32) to the amount of the compound (31) is at least an equimolar quantity, preferably an equimolar quantity to 5 times the molar quantity of the former to the latter.

20 Among the compounds represented by the general formula (32), some of them are novel compounds and they can prepared by a method for example according to the following reaction process formula-17.

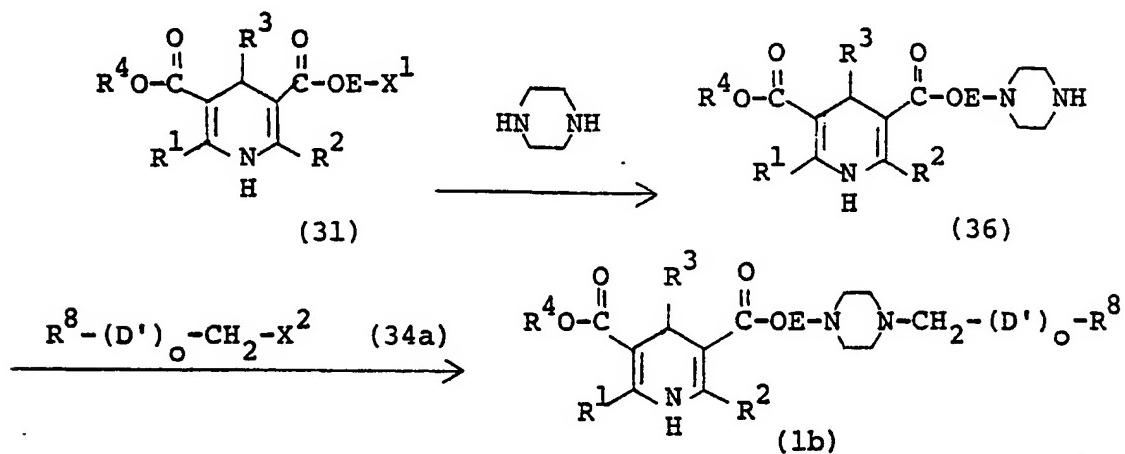
1 Reaction process formula-17



[wherein  $\text{R}^8$ ,  $\text{D}'$ ,  $\text{o}$  and  $\text{X}^1$  are the same as defined above; and  $\text{R}^{15}$  is a lower alkanoyl group].

- The reaction of a compound (33) with a compound  
 5 (34) can be carried out under the same condition  
 employed in the reaction of a compound (24) with a com-  
 pound (25), and the hydrolysis followed by the reaction  
 can be carried out under the same conditions employed  
 in the hydrolysis of a compound (3g) in the above-  
 10 mentioned reaction process formula-9.

Reaction process formula-18



- 1 [wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, E, X<sup>1</sup>, R<sup>8</sup>, D' and o are the same as defined above; and X<sup>2</sup> is a halogen atom].

The reaction of a compound (31) with piperazine can be carried out under the same conditions employed  
5 in the reaction of a compound (31) with a compound (32). Further, the reaction of a compound (36) with a compound (34a) can be carried out under the same conditions employed in the reaction of a compound (24) with a compound (25).

10 Among the compounds represented by the general formula (1), those having basic groups can be converted into the corresponding salts by treating with pharmaco- logically acceptable acids. Examples of such acids including inorganic acids such as sulfuric acid, nitric acid, hydrochloric acid, hydrobromic acid and others; as well as organic acids such as oxalic acid, maleic acid, fumaric acid, malic acid, citric acid, benzoic acid and others.

Compound of the present invention thus prepared can easily be isolated and purified by a method usually employed in separation, such as precipitation, extraction, recrystallization, column chromatography, preparative thin layer chromatography and others.

Compound of the present invention represented  
25 by the general formula (1) contains inevitably its optical isomers, as well as those in different crystal forms.

Compound of the present invention represented

- 1 by the general formula (1) can be administered, either singly or together with conventional pharmacologically acceptable carriers, to animals as well as to human beings. No particular restriction is made to the
- 5 administration unit forms, thus compound of the present invention represented by the general formula (1) can be used in any desired administration unit form. Suitable administration unit forms including peroral administration unit forms such as tablets, granules and solutions;
- 10 and parenteral administration unit forms such as injections.

Dosage of a compound represented by the general formula (1) as the active ingredient to be administered is not subjected to any particular restriction and can  
15 be selected from a wide range. For the purpose of attaining the desired pharmacological effects, it is recommended to select a dosage from the range of 0.06 to 10 mg/kg of the body weight/day. It is suggested also to contain 1 to 500 mg of the active ingredient in  
20 each of the desired administration unit form.

In the present invention, the desired peroral administration unit forms such as tablets, capsules and solutions can be prepared by conventional methods. For the purpose of shaping the administration unit form  
25 into the form of tablets, a compound of the present invention is mixed with pharmaceutically acceptable excipients such as gelatin, starch, lactose, magnesium stearate, talcum powder and gum arabic and others.

- 1 Capsules can be prepared by mixing a compound of the present invention with an inert pharmaceutically acceptable fillers or diluents and filling the mixture obtained into rigid gelatin capsules or soft capsules.
- 5 Sirups or elixiers may be prepared by mixing a compound of the present invention with a sweetening agent such as sucrose; anticeptice such as methyl- or propyl-parabens; colorants; seasoning agents and/or other suitable additives. Parenteral preparations can also
- 10 be prepared by conventional methods, thus a compound of the present invention is dissolved in a sterilized liquid vehicle. As to the preferable vehicle, water or saline can be used. Liquid preparations having desired transparency, stability and parenteral use adaptability
- 15 can be prepared by dissolving approximately 1 to 500 mg of the active ingredient in a solution of polyethylene glycol having the molecular weight of 200 to 5,000, which is soluble in both water and organic solvents. Desirably, such liquid preparations may contain a lubricant such
- 20 as sodium carboxymethyl cellulose, methyl cellulose, polyvinyl pyrrolidone and polyvinyl alcohol. Said liquid preparations may also contain a bactericide and fungicide such as benzyl alcohol, phenol and thimerosal, and if necessary, an isotonic agent such as sucrose or
- 25 sodium chloride, a local anesthetic, stabilizer and buffer solutions. Furthermore, additional ensurance of stability, the parenteral compositions may be freezed after filling and dehydrating steps by known lyophilization techniques.

- 1 The lyophilized powder of the parenteral composition can be made again into a normal use from just before the use.

Preparation of Tablets

- 1,000 Tablets for peroral use, each containing  
5 5 mg of methyl 3-(4-hydroxyphenyl)-2-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate are prepared from the following formulation.

<u>Formulation</u>	<u>Amount (g)</u>
Methyl 3-(4-hydroxyphenyl)-2-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate	5
Lactose (Japanese Pharmacopoeia official drug grade)	50
Corn starch (Japanese Pharmacopoeia official drug grade)	25
Crystalline cellulose (Japanese Pharmacopoeia official drug grade)	25
Methyl cellulose (Japanese Pharmacopoeia official drug grade)	1.5
Magnesium stearate (Japanese Pharmacopoeia official drug grade)	1

- Methyl 3-(4-hydroxyphenyl)-2-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate, lactose, corn starch and crystalline cellulose are mixed well, and the mixture is granulated with 5%-methyl cellulose aqueous solution, then the granules are passed through a 200 mesh sieve and then

1 dried carefully. The dried granules are passed through a 200 mesh sieve and mixed with magnesium stearate, then pressed into the form of tablets.

**Preparation of capsules**

5 1,000 Capsules of two-piece rigid gelatin capsules for peroral use, each containing 10 mg of methyl 3-(4-hydroxyphenyl)-2-propynyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate are prepared by using the following formulation.

<u>Formulation</u>	<u>Amount (g)</u>
Methyl 3-(4-hydroxyphenyl)-2-propynyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate	10
Lactose (Japanese Pharmacopoeia official drug grade)	80
Starch (Japanese Pharmacopoeia official drug grade)	30
Talcum powder (Japanese Pharmacopoeia official drug grade)	5
Magnesium stearate (Japanese Pharmacopoeia official drug grade)	1

10 The above-mentioned ingredients are finely ground, then mixed sufficiently to a uniform mixture and filled into gelatin capsules of a size having desired size for peroral administration.

1 Preparation of injection solution

A sterile aqueous solution suitable for parenteral use is prepared from the following formulation.

<u>Formulation</u>	<u>Amount (g)</u>
Methyl 3-(4-hydroxyphenyl)-2-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate	1
Polyethylene glycol (M. W. = 4,000) (Japanese Pharmacopoeia official drug grade)	0.9
Sodium chloride (Japanese Pharmacopoeia official drug grade)	0.9
Polyoxyethylene sorbitan monooleate (Japanese Pharmacopoeia official drug grade)	0.4
Sodium metabisulfite	0.1
Methyl p-hydroxybenzoate (Japanese Pharmacopoeia official drug grade)	0.18
Propyl p-hydroxybenzoate (Japanese Pharmacopoeia official drug grade)	0.02
Distilled water for injection	100 (ml)

The above-mentioned methyl p-hydroxybenzoate,  
5 propyl p-hydroxybenzoate, sodium metabisulfite and sodium chloride are dissolved in about a half volume of distilled water at 80°C under stirring condition. The solution obtained is cooled to 40°C, then methyl 3-(4-hydroxyphenyl)-2-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate, polyethylene glycol and polyoxyethylene sorbitan monooleate are dissolved in the solution. Thus obtained solution is

1 further mixed with the distilled water for injection so  
as to make it into the final volume, then sterilized by  
sterile filtration with a suitable filter paper.

The present invention will be illustrated more  
5 specifically by way of the following examples, in which  
the preparations of the compounds to be used for the  
starting materials will be shown in Reference Examples  
and the preparations of the objective compounds will be  
shown in Examples. The present invention, however will  
10 not restricted to these examples.

Reference Example 1

To 20 g of p-hydroxybenzaldehyde and 32.5 g  
of monoethyl malonate were added 6 ml of pyridine and  
0.2 ml of piperidine, then the mixture thus obtained was  
15 heated at 100 to 110°C for 10 hours under stirring.  
The reaction mixture was then cooled, extracted with  
chloroform, and the chloroform layer was washed with a  
saturated aqueous solution of potassium hydrogen sulfite  
and water in this order, the chloroform extract was  
20 dried with magnesium sulfate. The solvent was removed  
by evaporation and the residue thus obtained was crystal-  
lized from isopropyl ether-n-hexane to yield 25.2 g of  
ethyl 4-hydroxycinnamate. Light yellow indefinite form  
crystals. Melting point: 70 - 71°C.

25 Reference Example 2

By using 20 g of 3-hydroxybenzaldehyde and

1 32.5 g of monoethyl malonate as the starting materials, and by a method similar to that described in Reference Example 1, under reaction conditions similar thereto, there was prepared 25.5 g of ethyl 3-hydroxycinnamate.

5 Melting point: 65 - 68°C. (from isopropyl ether)

Reference Example 3

By using 25.8 g of 4-hydroxy-3-chlorobenzaldehyde and 32.5 g of monoethyl malonate as the starting materials, and by a method similar to that described in Reference

10 Example 1, under reaction conditions similar thereto, there was prepared 46 g of ethyl 4-hydroxy-3-chlorocinnamate. Colorless prism-like crystals (from methylene chloride). Melting point: 118 - 119°C.

Reference Example 4

15 To 30 ml of anhydrous ether solution containing 5 g of ethyl 4-hydroxycinnamate was added 7.1 ml of dihydropyran and 50 mg of p-toluenesulfonic acid were added, the mixture was stirred at a room temperature for 2 hours, the reaction mixture was neutralized with 20 1%-sodium hydroxide solution, washed with water, and dried with anhydrous sodium sulfate. The solvent was removed by evaporation to yield 6.8 g of ethyl 4-(2-tetrahydropyranyloxy)cinnamate. Colorless indefinite form crystals. Melting point: 52 - 53°C.

1 Reference Example 5

50 Milliliters of anhydrous ether solution containing 6.8 g of ethyl 4-(2-tetrahydropyranyloxy)-cinnamate was added dropwise to an anhydrous ether solution containing 0.47 g of lithium aluminium hydride being cooled at -30°C. After the addition was finished, the reaction mixture was stirred for 1 hour at the same temperature, then the temperature of the reaction mixture was gradually elevated up to -10°C, then a saturated aqueous solution of sodium sulfate was gradually added to the reaction mixture, and the precipitates formed were removed by filtration. The filtrate was dried with anhydrous sodium sulfate, then concentrated to dryness, the residue thus obtained was treated by means of silica gel column chromatography (eluent: chloroform) to yield 3.2 g of 4-(2-tetrahydropyranyloxy)cinnamyl alcohol in the form of colorless oily substance. Refractive index:  $n_D^{22}$  1.5520.

Reference Example 6

20 15 Grams of 4-(2-tetrahydropyranyloxy)cinnamyl alcohol and 5.2 g of sodium acetate were suspended in anhydrous methylene chloride, then to this suspension was added in one time 18 g of pyridium chlorochromate under ice-cooled condition. The reaction mixture was stirred for 1 hour at the same temperature, then the temperature was elevated to a room temperature, and the reaction mixture was stirred for additional 1 hour.

1 100 Milliliters of ether was added to the reaction mixture, the whole mixture was filtered with Celite (a trademark for diatomaceous product manufactured by and sold from Johns-Manville Products Corp., Celite Division, 5 New York, N. Y., U. S. A.), the filtrate was concentrated and the residue thus obtained was treated by silica gel column chromatography. Recrystallization from ether to yield 3.5 g of 4-(2-tetrahydropyranyloxy)-cinnamyl aldehyde in the form of colorless needle-like 10 crystals. Melting point: 65 - 67°C.

Reference Example 7

5.6 Grams of triethyl phosphonoacetate was added dropwise under stirring condition at a room temperature to a tetrahydrofuran solution containing 1.06 g 15 of 60%-sodium hydride, then the reaction mixture was further stirred at 40°C for 1 hour. The reaction mixture was cooled to a room temperature, then a tetrahydrofuran solution containing 5.6 g of 4-(2-tetrahydropyranyloxy)-cinnamyl aldehyde was added thereto, and stirred at a 20 room temperature for 2 hours, then the reaction mixture was poured into 100 ml of water. The whole mixture was extracted with ether, and the ether layer was washed with water, and a saturated aqueous solution of sodium chloride in this order, then dried with anhydrous sodium 25 sulfate. Recrystallization from isopropyl ether to yield 3.8 g of ethyl 5-[4-(2-tetrahydropyranyloxy)phenyl]-2(E),4(E)-pentadienoate in the form of colorless needle-like

1 crystals. Melting point: 66 - 67.5°.

Reference Example 8

To 30 ml of anhydrous benzene solution containing 3.6 g of ethyl 5-[4-(2-tetrahydropyranyloxy)phenyl]-2(E),4(E)-pentadienoate was added dropwise 15 ml of diisobutyl aluminium hydride (25% by weight/by volume) under water-cooled condition and the reaction mixture was stirred at a room temperature for 2 hours. The reaction mixture was then poured into a saturated aqueous solution of ammonium chloride and stirred at a room temperature for 2 hours. The insoluble matters were treated with Celite, and the insoluble matters were washed with ether. The organic layer was washed with water and dried with anhydrous sodium sulfate, then concentrated to obtain the residue. The residue was recrystallized from chloroform-n-hexane to yield 2.8 g of 5-[4-(2-tetrahydropyranyloxy)phenyl]-2(E),4(E)-pentadienol in the form of colorless needle-like crystals.

Melting point: 54 - 58°C.

20 Reference Example 9

25 Grams of p-hydroxyacetophenone, 50 ml of dihydropyran and 0.25 g of p-toluenesulfonic acid were stirred at a room temperature for 2 hours in anhydrous ether. Then the reaction mixture was neutralized with 1N-sodium hydroxide and washed with water and a saturated sodium chloride aqueous solution in this order, then

1 dried with anhydrous sodium sulfate. The product was concentrated to yield 34 g of 4-(2-tetrahydropyranloxy)-acetophenone. Colorless prism-like crystals. Melting point: 79 - 83°C.

5 Reference Example 10

45.8 Grams of triethyl phosphonoacetate and an anhydrous tetrahydrofuran solution containing 8.7 g of 60%-sodium hydride were stirred at 40°C for 1 hour, the reaction mixture was cooled and 30 g of 4-(2-tetra-  
10 hydropyranloxy)acetophenone was added to the reaction mixture. The whole reaction mixture was refluxed for 4 hours by heating, then the solvent was removed by evaporation, the residue thus obtained was extracted with ether and washed with water, than dried. The  
15 extract was concentrated and the residue thus obtained was treated by means of silica gel column chromatography to yield 27.5 g of ethyl 3-methyl-p-(2-tetrahydropyranloxy)cinnamate in the form of light yellow oily substance.

$^1\text{H-NMR}$  (90 MHz,  $\text{CDCl}_3$ )  $\delta$ :

1.29 (3H, t,  $J=6\text{Hz}$ ), 1.4 - 2.1 (6H, m),  
2.49 (3H, d,  $J=1\text{Hz}$ ), 3.3 - 3.9 (2H, m),  
4.10 (2H, q,  $J=6\text{Hz}$ ), 5.3 - 5.45 (1H, m),  
6.03 (1H, d,  $J=1\text{Hz}$ ), 6.9 - 7.4 (4H, m)

Reference Example 11

20 To a tetrahydrohydrofuran solution containing 27.5 g of ethyl 3-methyl-p-(2-tetrahydropyranloxy)-

1 cinnamate was added dropwise 118 ml of diisobutyl  
aluminium hydride (25% by weight/volume) at a room  
temperature. After 2 hours, the reaction mixture was  
poured into an ice-cooled ammonium chloride aqueous  
5 solution, and the insoluble matters were removed by  
filtration. The filtrate was washed with water then  
dried with anhydrous sodium sulfate and concentrated.  
The residue thus obtained was purified by means of silica  
gel column chromatography to yield 12.7 g of 3-methyl-p-  
10 (2-tetrahydropyranloxy)cinnamyl alcohol in the form of  
colorless oily substance.

$^1\text{H-NMR}$  (90 MHz,  $\text{CDCl}_3$ )  $\delta$ :

1.5 - 2.0 (6H, m), 2.0 (3H, s),  
3.3 - 4.0 (2H, m), 4.1 - 4.3 (3H, m), 5.26 -  
5.4 (1H, m), 5.81 (1H, t,  $J=6\text{Hz}$ ), 6.8 - 7.5  
(4H, m).

#### Reference Example 12

To a carbon disulfide solution containing 53 g  
of aluminium chloride and 26.2 g of thioanisol was added  
15 dropwise under an ice-cooled condition 24.0 ml of  $\gamma$ -  
chlorobutyryl chloride. After 1 hour and 30 minutes,  
the reaction mixture was poured into ice-water and the  
insoluble matters were collected by filtration, dis-  
solved in chloroform. The chloroform solution was  
20 washed with water and dried with anhydrous sodium sulfate,  
and concentrated to dryness. Recrystallization from  
methanol to yield 36.2 g of  $\gamma$ -chloro-4-methylthiobutyro-

1 phenone in the form of light yellow prism-like crystals.  
Melting point: 75 - 76°C.

Reference Example 13

35 Grams of  $\gamma$ -chloro-4-methylthiobutyrophenone,  
5 34 ml of 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) and  
150 ml of acetonitrile were refluxed for 4 hours, then  
500 ml of water was added to the reaction mixture, and  
the whole mixture was extracted with ether. The ether  
extract was washed with water, dried and the solvent  
10 was removed by evaporation. The residue thus obtained  
was recrystallized from methanol to yield 24.6 g of  
cyclopropyl (4-methylthiophenyl)ketone as in the form  
of light yellow prism-like crystals. Melting point:  
76 - 76.5°C.

15 Reference Example 14

To 200 ml of methanol solution containing 24 g  
of cyclopropyl (4-methylthiophenyl)ketone was added  
slowly 9.4 g of sodium borohydride under an ice-cooled  
condition, the reaction mixture was stirred for 2 hours.  
20 Then an adequate amount of acetone was added to the  
reaction mixture and concentrated under a reduced pres-  
sure. To the residue thus obtained was added chloroform,  
and the chloroform solution was washed with water,  
dried with anhydrous sodium sulfate, and the solvent was  
25 removed by evaporation to yield 18 g of 1-(cyclopropyl,  
hydroxymethyl)-4-methylthiobenzene as in the form of

1 colorless oily substance.

NMR (90 MHz, CDCl<sub>3</sub>) δ:

0.2 - 0.7 (4H, m), 0.9 - 1.4 (1H, m), 1.4 - 2.0  
(6H, m), 3.2 - 3.7 (2H, m), 5.17 - 5.3 (1H, m),  
6.8 - 7.3 (8H, m).

Reference Example 15

To 10 ml of dioxane solution containing 5 g of 1-(cyclopropyl, hydroxymethyl)-4-methylthiobenzene was 5 added dropwise 6 ml of 47% of hydrobromic acid under an ice-cooled condition, then the mixture was stirred for 30 minutes, and the reaction mixture was concentrated under a reduced pressure. To the residue thus obtained was added water, then extracted with ether, the extract 10 was washed with water and dried with anhydrous sodium sulfate, and concentrated to dryness. The residue was recrystallized from methanol to yield 2.2 g of 4-(4'-methylthiophenyl)-3(E)-butenylbromide in the form of colorless flake-like crystals. Melting point: 54 - 56°C.

15 Reference Example 16

10 Grams of p-iodophenol, 8 ml of dihydropyran and a catalytic amount of p-toluenesulfonic acid was dissolved in 30 ml of anhydrous ether, all of these were mixed together and stirred at a room temperature for 2 20 hours. The reaction mixture was washed with water, dried then the solvent was removed by evaporation to yield 12.4 g of 4-(2-tetrahydropyranyloxy)-1-iodobenzene

1 in the form of yellow oily substance. Boiling point:  
84 - 87°C (at 25 mm Hg).

Reference Example 17

6.25 Grams of triethyl phosphonocrotonate was  
5 added dropwise to a tetrahydrofuran solution containing  
1.06 g of 60%-sodium hydride at a room temperature, the  
reaction mixture was stirred for 1 hour at 40°C. The  
temperature of the reaction mixture was cooled to a room  
temperature, then a tetrahydrofuran solution containing  
10 5.0 g of p-(2-tetrahydropyranyloxy)benzaldehyde was  
added to the reaction mixture, and stirred at a room  
temperature for 2 hours, then poured into 100 ml of  
water. The whole mixture was extracted with ether,  
the ether extract was washed with water and a saturated  
15 sodium chloride aqueous solution in this order, then  
dried with anhydrous sodium sulfate. The solvent was  
removed by evaporation, the residue thus obtained was  
purified by means of silica gel column chromatography  
(eluent: hexane-chloroform), next recrystallized from  
20 isopropyl ether to yield 4.01 g of ethyl 5-[4-(2-tetra-  
hydropyranyloxyphenyl)]-2(E),4(E)-pentadienoate. Colorless  
needle-like crystals. Melting point: 66 - 67.5°C.

Reference Example 18

20 Grams of p-tetrahydropyranyloxyiodobenzene  
25 and 70 ml of anhydrous pyridine containing 11.3 g of  
copper (I) 3-acetyloxy-1-propyn-1-ide were refluxed for

1 6 hours under an atmosphere of argon gas. After the  
reaction was finished the reaction mixture was poured  
into water and the whole mixture was extracted with  
chloroform. The chloroform layer was washed with water,  
5 dried and the solvent was removed by evaporation. The  
residue thus obtained was purified by means of a silica  
gel column chromatography (eluent: chloroform: n-hexane =  
1:1) to yield 8 g of 4-[4-(2-tetrahydropyranyloxy)phenyl]-  
3-butynyl acetate in the form of colorless oily substance.

<sup>1</sup>H-NMR (60 MHz, CDCl<sub>3</sub>) δ:

6.98 (2H, d, J=8Hz), 6.63 (2H, d, J=8Hz),  
6.15 (1H, m), 4.05 (2H, t, J=6Hz), 3.3 - 3.7  
(2H, m), 2.58 (2H, t, J=6Hz), 1.97 (3H, s),  
1.5 - 1.9 (6H, m).

10 Reference Example 19

To an anhydrous tetrahydrofuran solution containing 2.4 g of 4-[4-(2-tetrahydropyranyloxy)phenyl]-3-butynylacetate was added 1 g of lithium aluminium hydride and the mixture was refluxed for 12 hours. After 15 the reaction was finished, a saturated sodium sulfate aqueous solution was slowly added to the reaction mixture, and the precipitates formed were removed by filtration, then the filtrate was dried with anhydrous sodium sulfate, and concentrated to dryness. The residue 20 thus obtained was purified by means of a silica gel column chromatography to yield 2 g of 4-[(2-tetrahydropyranyloxy)phenyl]-3(E)-butenylalcohol as in the form

1 of colorless oily substance.

<sup>1</sup>H-NMR (90 MHz, CDCl<sub>3</sub>) δ:

1.5 - 2.1 (6H, m), 2.43 (2H, q, J=6Hz),  
3.4 - 4.0 (5H, m), 5.37 (1H, m), 6.03 (1H, d, t,  
J=16Hz, 6Hz), 6.40 (1H, d, J=16 Hz), 6.97 (2H,  
d, J=9Hz), 7.25 (2H, d, J=9Hz).

Reference Example 20

15 Grams of 1-iodo-4-(1-ethoxyethoxy)benzene,  
6 g of propargyl acetate, 0.26 g of triphenylphosphine,  
5 0.09 g of palladium chloride and 20 ml of diethylamine  
solution of cuprous iodide were stirred at 40 - 50°C for  
1 hour. After the reaction was finished, the reaction  
mixture was poured into water, and extracted with diethyl  
ether. The ether extract was washed with water, dried  
10 and the solvent was removed by evaporation, then the  
residue thus obtained was purified by means of a silica  
gel column chromatography (eluent: dichloromethane:  
n-hexane = 1:1 and dichloromethane) to yield 10.1 g of  
3-[4-(1-ethoxyethoxy)phenyl]propargyl acetate.

N. M. R. (CDCl<sub>3</sub>) δ:

1.17 (3H, t, J=7Hz), 1.47 (3H, d, J=5Hz),  
2.09 (3H, s), 3.3 - 3.9 (2H, m), 4.87 (2H,  
s), 5.37 (1H, q, J=5Hz), 6.92 (2H, d, J=9Hz),  
7.37 (2H, q, J=9Hz).

15 Reference Example 21

To 50 ml of methanol solution containing 10 g

1 of 3-[4-(1-ethoxyethoxy)phenyl]propargyl acetate, were  
added 1.5 g of 5%-Pd-BaSO<sub>4</sub> and 10 drops of quinoline,  
and the mixture was catalytically reduced. After the  
reaction was finished, the reaction mixture was filtered,  
5 and the filtrate was allowed to evaporation, the residue  
thus obtained was purified by means of a silica gel  
column chromatography (eluent: dichloromethane and  
dichloromethane:methanol = 100:1) to obtain 3 g of  
4(Z)-(1-ethoxyethoxy)cinnamyl acetate and 4 g of 4(Z)-  
10 hydroxycinnamyl acetate. Thus obtained 4 g of 4(Z)-  
hydroxycinnamyl acetate was dissolved in 20 ml of  
anhydrous ether, to this solution was added 50 mg of p-  
toluenesulfonic acid and 10 ml of ethyl vinyl ether, and  
the whole mixture was refluxed for 3 hours. The reaction  
15 mixture was then washed with 5%-sodium hydroxide aqueous  
solution and water in this order, and dried. The solvent  
was removed by evaporation to yield 4.8 g of 4(Z)-(1-  
ethoxyethoxy)cinnamyl acetate.

N. M. R. (CDCl<sub>3</sub>) δ:

1.21 (3H, t, J=7Hz), 1.50 (3H, d, J=5Hz),  
2.09 (3H, s), 3.24 - 3.64 (1H, m), 3.70 - 3.90  
(1H, m), 4.84 (2H, dd, J=6.5Hz, 1.5Hz), 5.40  
(1H, q, J=5Hz), 5.73 (1H, dt, J=11.5Hz,  
6.5Hz), 6.60 (1H, dm, J=11.5Hz), 6.98 (2H, d,  
J=9Hz), 7.15 (2H, d, J=9Hz).

Reference Example 22

1 acetate and 50 ml of methanol solution containing 5 g of potassium carbonate were stirred at a room temperature for 2 hours. The solvent was removed by evaporation, and to the residue thus obtained was added water and  
5 extracted with ether. The ether extract was washed with water, dried and the solvent remove by evaporation to yield 4(Z)-(1-ethoxyethoxy)cinnamyl alcohol.

N. M. R. (90 MHz,  $\text{CDCl}_3$ )  $\delta$ :

1.19 (3H, t,  $J=7\text{Hz}$ ), 1.48 (3H, d,  $J=5\text{Hz}$ ),  
3.4 - 3.9 (2H, m), 4.39 (2H, dd,  $J=6\text{Hz}$ ,  $J=2\text{Hz}$ ),  
5.36 (1H, q,  $J=5\text{Hz}$ ), 5.75 (1H, dt,  $J=11\text{Hz}$ ,  
 $J=6\text{Hz}$ ), 6.45 (1H, dm,  $J=11\text{Hz}$ ), 6.95, 7.10 (4H,  
AB-q,  $J=9\text{Hz}$ ).

Reference Example 23

8 Milliliters of 85% sodium hydroxide aqueous  
10 solution mixed with 46 g of ethylene glycol was heated at 40 - 50°C, and 15 g of cinnamyl bromide was added dropwise thereto. After the addition was finished, the reaction mixture was heated at 100 - 110°C for 2 hours. The reaction mixture was allowed to cool, and poured  
15 into 50 ml of water, then extracted with ether. The ether extract was washed with water and a saturated aqueous solution of sodium chloride in this order, and dried with anhydrous sodium sulfate. The solvent was removed by evaporation, the residue thus obtained was  
20 purified by means of a silica gel column chromatography (eluent: chloroform) to yield 5.5 g of 2-[3-phenyl-

1 2(E)-propenyoxy]ethanol.

N. M. R. CDCl<sub>3</sub> (90 MHz) δ:

2.20 (1H, t, J=6Hz), 3.50 - 3.85 (4H, m),  
4.18 (2H, d, J=6Hz), 6.23 (1H, dt, J=6Hz,  
J=16Hz), 6.57 (1H, d, J=16Hz), 7.20 - 7.50  
(5H, m).

Reference Example 24

5.33 Grams of 60% sodium hydride was suspended in 25 ml of dimethylformamide, and 9.3 ml of ethylene 5 glycol was added dropwise thereto. After the addition was finished the reaction mixture was stirred at 45°C for 2 hours. The reaction mixture was ice-cooled, then 6.5 g of 3-phenylpropargyl bromide was added dropwise to the reaction mixture and stirred at the same temperature 10 for 1 hour. After the reaction was finished, the reaction mixture was poured into 200 ml of water, and the whole mixture was extracted with ether. The ether extract was washed with water and dried with anhydrous magnesium sulfate, and the solvent was removed by evaporation. The 15 residue thus obtained was purified by means of a silica gel column chromatography (eluent: chloroform:n-hexane = 3:1) to yield 2.4 g of 2-(3-phenyl-2-propionyloxy)ethanol. Refractive index: n<sub>D</sub><sup>24</sup> 1.5590.

Reference Example 25

20 6.5 Grams of propargyl bromide, 0.32 g of tetra-butylammonium bromide and 2.7 g of sodium hydroxide were

1 dissolved in 20 ml of methylene chloride and 8 ml of water, and this solution was refluxed for 2 hours. After the reaction mixture was cooled, the organic layer was collected by separation, washed with water, dried with  
5 anhydrous magnesium sulfate. The solvent was removed by evaporation, the residue thus obtained was purified by means of a silica gel column chromatography (eluent: chloroform:n-hexane = 2:1) to yield 4.0 g of 2-(3-phenyl-2-propionylthio)ethanol. Refractive index:  
10  $n_D^{22}$  1.6078.

Reference Example 26

4.3 Grams of 2-mercaptoethanol, 10 ml of 40% sodium hydroxide aqueous solution, 0.2 g of tetrabutyl-ammonium bromide and 40 ml of methylene chloride were  
15 heated at 40 - 45°C, then 20 ml of methylene chloride solution containing 10 g of cinnamyl bromide was added dropwise thereto. The reaction mixture was stirred vigorously at the same temperature for 4 - 5 hours. The organic layer was collected by separation and washed with  
20 water, dried with anhydrous sodium sulfate. The solvent was removed by evaporation, the residue thus obtained was distilled under a reduced pressure to yield 8.6 g of 2-(3-phenyl-2(E)-propionylthio)ethanol. Boiling point: 150 - 153°C (1 mm Hg).

N. M. R.  $\text{CDCl}_3$  (90 MHz)  $\delta$ :

2.16 (1H, t, J=6Hz), 2.70 (2H, t, J=6Hz),  
3.30 (2H, d, J=6Hz), 3.70 (2H, q, J=6Hz),

6.14 (1H, dt, J=6Hz, J=16Hz), 6.40 (1H, d,  
J=16Hz), 7.20 - 7.60 (5H, m).

1 Reference Example 27

12.5 Grams of cinnamyl chloride and 21 g of 2-methylaminoethanol were dissolved in 100 ml of ethanol, and the solution was refluxed for 5 hours. The solvent 5 was removed by evaporation, to the residue thus obtained was added water and washed with n-hexane. To the water layer was added 3N-sodium hydroxide aqueous solution to adjust its pH to 10 - 11, and extracted with ether. The ether extract was washed with water and dried with 10 anhydrous sodium sulfate, and the solvent was removed by evaporation. The residue was purified by means of a silica gel column chromatography (eluent: chloroform: methanol = 25:1) to yield 15 g of 2-[N-methyl-N-(3-phenyl-2(E)-propenyl)amino]ethanol.

N. M. R. CDCl<sub>3</sub> (90 MHz) δ:

2.30 (3H, s), 2.55 (2H, t, J=7Hz), 2.90 (1H, s),  
3.20 (2H, d, J=7Hz), 3.60 (2H, t, J=7Hz),  
6.20 (1H, dt, J=7Hz, J=16Hz), 6.48 (1H, d,  
J=16Hz), 7.25 - 7.50 (5H, m).

15 Reference Example 28 .

By a method similar to that described in Reference Example 27, by using a suitable starting material, the following compound was prepared.

2-[N-Methyl-N-(3-phenyl-2-propynyl)amino]ethanol

Boiling point: 124 - 126°C (1m2 mm Hg)

Refractive index:  $n_D^{24}$  1.5589

1 Reference Example 29

5 Grams of cinnamyl bromide, 5 g of anhydrous piperazine and 50 ml of acetone solution containing 8.4 g of anhydrous potassium carbonate were refluxed for 5 6 hours. To the reaction mixture was added water and the whole mixture was extracted with chloroform. The chloroform layer was washed with water, dried and the solvent was removed by evaporation. 2.2 Grams of 1-acetyl-4-cinnamylpiperazine thus obtained was dissolved 10 in 80% of methanol, and 2 g of potassium hydroxide was added thereto, then the mixture was refluxed for 8 hours. To the reaction mixture was added water, and the whole mixture was extracted with chloroform, washed with water, dried, and chloroform was removed by evaporation. The 15 residue thus obtained was purified by means of a silica gel column chromatography (eluent: chloroform and chloroform:methanol = 30:1) to yield 1.2 g of N-cinnamyl-piperazine.

N. M. R.  $\text{CDCl}_3$  δ:

2.34 (1H, s), 2.46 (4H, m, J=5Hz), 2.92 (4H, m, J=5Hz), 3.13 (2H, d, J=6Hz), 6.23 (1H, dt, J=15Hz, 6Hz), 6.82 (1H, d, J=15Hz), 7.2 - 7.5 (5H, m).

1 Reference Example 30

To 150 ml of anhydrous carbon tetrachloride solution containing 116 g of methyl acetoacetate was added dropwise 51 ml of bromine at below 5°C. After the 5 addition was finished the reaction mixture was stirred overnight, then the reaction mixture was poured into ice-water, washed with a diluted sodium carbonate aqueous solution five times, then with a saturated sodium chloride aqueous solution, and dried with anhydrous calcium 10 chloride. The solvent was removed by evaporation to yield 170 g of methyl 4-bromoacetoacetate.

Reference Example 31

1.6 Grams of 60% sodium hydride was suspended in 80 ml of anhydrous dimethoxyethane, then 40 ml of 15 dimethoxyethane solution containing 8 g of methyl 4-bromoacetoacetate was added dropwise thereto at -40 to -50°C. At the same temperature, lithium N-methylcinnamyl-amide prepared from 20 ml of dimethoxyethane solution containing 5.9 g of N-methylcinnamylamine and 40 ml of 20 1N-n-butyl lithium was added dropwise. After the addition was finished, the reaction mixture was stirred at 65 - 70°C for 15 hours. The reaction mixture was poured into an ice-water and the whole mixture was extracted with diethyl ether. The extract was washed with water, dried 25 and the solvent was removed by evaporation, the residue thus obtained was purified by means a silica gel column chromatography (eluent: dichloromethane and dichloro-

1   methane:methanol = 50:1) to yield 1.8 g of 4-(N-methyl-E-cinnamylamino)acetoacetate.

N. M. R.  $\text{CDCl}_3$   $\delta$ :

2.32 (3H, s), 3.22 (2H, d,  $J=6\text{Hz}$ ), 3.31 (2H, s),  
3.51 (2H, 2), 3.68 (3H, s), 6.18 (1H, dt,  
 $J=16\text{Hz}$ , 6Hz), 6.50 (1H, d,  $J=16\text{Hz}$ ), 7.0 - 7.5  
(5H, m).

Reference Example 32

4 Grams of 60% sodium hydride was suspended in  
5 150 ml of anhydrous dimethoxyethane and the suspension  
was cooled to  $-30^\circ\text{C}$ . Then, 19.4 g of methyl 4-bromo-  
acetoacetate was added dropwise to the suspension and  
stirred for 1 hour. Further, at the same temperature, an  
anhydrous dimethoxyethane solution of sodium cinnamyl  
10 alcoholate prepared from 13.4 g of cinnamyl alcohol, 4 g  
of 60% of sodium hydride and 75 ml of dimethoxyethane  
was added dropwise thereto, and the reaction mixture was  
refluxed for 15 hours. After the reaction mixture was  
cooled to a room temperature, the reaction mixture was  
15 poured into 1N-hydrochloric acid being ice-cooled, and  
the whole mixture was extracted with ether. The ether  
extract was washed with water and dried with anhydrous  
sodium sulfate, and the solvent was removed by evaporation.  
The residue was purified by means of a silica gel column  
20 chromatography (eluent: methanol:dichloromethane = 1:20)  
to yield 6 g of methyl 4(E)-cinnamyloxyacetoacetate  
Refractive index:  $n_D^{20}$  1.5402

1 Reference Example 33

By a method similar to that described in Example 32, by using a suitable starting material, there was prepared the following compounds.

Methyl 4-[4(E)-(1-ethoxyethoxy)cinnamyloxy]-acetoacetate

Refractive index:  $n_D^{20} = 1.5232$

5 Reference Example 34

A mixture of 9 g of 4(E)-(1-ethoxyethoxy)-cinnamyl alcohol and 0.5 ml of triethylamine was heated at 70 - 80°C, and 6 g of diketene was slowly added dropwise thereto. After the addition was finished, the reaction mixture was heated at 110 - 120°C for 30 minutes. After the reaction was completed, the solvent was removed by evaporation under a reduced pressure, and the residue thus obtained was purified by means of a silica gel column chromatography (eluent: diethyl ether: n-hexane = 1:3) to yield 8.8 g of 4(E)-(1-ethoxyethoxy)cinnamyl acetoacetate. Refractive index:  $n_D^{24} 1.5305$

N. M. R.  $\text{CDCl}_3$  (90 MHz) δ:

1.17 (3H, t, J=7Hz), 1.48 (3H, d, J=6Hz),  
2.25 (3H, s), 3.48 (2H, s), 3.40 - 3.85 (2H, m),  
4.75 (2H, d, J=6Hz), 5.36 (1H, q, J=6Hz),  
6.18 (1H, dt, J=6Hz, J=16Hz), 6.94 (2H, d,  
J=9Hz), 7.28 (2H, d, J=9Hz).

1 Reference Example 35

To 400 ml of acetonitrile solution containing 30 g of 2-iodoethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate was added 26.6 g 5 of piperazine, and the mixture was stirred at a room temperature overnight. After the reaction was finished, the insoluble matters were removed by filtration, then chloroform was added to the filtrate, the chloroform layer was washed with a saturated sodium hydrogen carbonate 10 aqueous solution and water in this order, and dried with anhydrous sodium sulfate. The reaction mixture was concentrated by evaporating the solvent, and the residue thus obtained was purified by means of a silica gel column chromatography (eluent: dichloromethane:methanol:tri- 15 ethylamine = 100:10:1) to yield 21 g of methyl 5-[2-(1-piperazinyl)ethyl] 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate as in the form of light yellow indefinite form crystals.

N. M. R.  $\text{CDCl}_3$  (200 MHz)  $\delta$ :

1.892 (1H, bs), 2.366 (3H, s), 2.379 (3H, s),  
2.40 - 2.50 (4H, m), 2.52 - 2.60 (2H, m),  
2.80 - 2.90 (4H, m), 3.651 (3H, s), 4.08 -  
4.28 (2H, m), 5.109 (1H, s), 5.947 (1H, bs),  
7.3 - 8.2 (4H, m).

Reference Example 36

20 18.6 Grams of 5-acetyl-2,2-dimethyl-1,3-dioxane-4,6-dione and 50 ml tetrahydrofuran solution containing

1 22.2 g of 4-(1-ethoxyethoxy)cinnamyl alcohol were refluxed for 6 hours. After the reaction was completed, the solvent was removed by evaporation, and the residue thus obtained was purified by means of a silica gel

5 column chromatography (eluent: ethyl acetate:n-hexane = 1:4) to yield 5.8 g of 4-[(1-ethoxy)ethoxy]cinnamyl acetoacetate as in the form of an oily substance.

N. M. R. ( $\text{CDCl}_3$ )  $\delta$ :

1.15 (3H, t,  $J=7\text{Hz}$ ), 1.44 (3H, d,  $J=5.4\text{Hz}$ ),  
2.20 (3H, s), 3.31 - 3.95 (2H, m), 3.45 (2H,  
s), 4.71 (2H, d,  $J=6\text{Hz}$ ), 5.35 (1H, q,  $J=5.2\text{Hz}$ ),  
6.10 (1H, dt,  $J=6.1\text{Hz}$ ,  $15.3\text{Hz}$ ), 6.59 (1H, d,  
 $J=15.3\text{Hz}$ ), 6.91 (2H, d,  $J=9\text{Hz}$ ), 7.29 (2H, d,  
 $J=9\text{Hz}$ ).

IR (film):  $\nu$  :  $1650, 1730^{-1}$ .

#### Example 1

5.4 Grams of 4-(2-tetrahydropyranloxy)cinnamyl  
10 alcohol, 11.5 g of 1,4-dihydro-2,6-dimethyl-5-methoxy-  
carbonyl-4-(3-nitrophenyl)pyridine-3-carboxylic acid and  
7.1 g of DCC were dissolved in 30 ml of pyridine, and  
the reaction mixture was stirred at a room temperature  
overnight. 200 Milliliters of water was added to the  
15 reaction mixture and extracted with ethyl acetate. The  
extract was washed with water, a saturated potassium  
hydrogen sulfate aqueous solution, water and a saturated  
sodium chloride aqueous solution in this order, then  
dried and the solvent was removed by evaporation. The

1 residue thus obtained was purified by means a silica gel column chromatography (eluent: chloroform) to yield 3.4 g of methyl 3-(4-tetrahydropyranloxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-5 pyridine-3,5-dicarboxylate.

N. M. R. δ (CDCl<sub>3</sub>):

1.4 - 2.0 (6H, m), 2.26 (6H, m), 3.53 (3H, s),  
3.4 - 4.0 (2H, m), 4.58 (2H, d, J=6Hz), 5.03  
(1H, s), 5.30 (1H, t, J=3Hz), 5.97 (1H, dt,  
Ja=6Hz, Jb=16Hz), 6.30 (1H, bs), 6.37 (1H, d,  
J=16Hz), 6.88 (2H, d, J=9Hz), 7.14 (2H, d,  
J=9Hz), 7.20 (1H, t, J=6Hz), 7.50 (1H, dt,  
Ja=2Hz, Jb=6Hz), 7.82 (1H, dt, Ja=2Hz, Jb=tHz),  
8.00 (1H, t, J=2Hz).

Example 2

3.4 Grams of methyl 3-(4-tetrahydropyranloxy-phenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate was dissolved in 10 50 ml of methanol, then 0.2 g of p-toluenesulfonic acid was added to the solution and the whole mixture was stirred at a room temperature for 4 hours. The reaction mixture was neutralized by adding sodium hydrogen carbonate, and methanol was removed by evaporation. The 15 residue thus obtained was purified by means of a silica gel column chromatography (eluent: chloroform), recrystallized from benzene-ether to yield 2 g of methyl 3-(4-hydroxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-

1 (3-nitrophenyl)pyridine-3,5-dicarboxylate as in the form  
of light yellow powdery substance. Melting point: 137.5 -  
139°C.

Example 3

5 To 20 ml of an anhydrous methylene chloride  
solution containing 1.6 g of tetramethylurea was added  
1.9 g of oxalyl chloride at a room temperature and the  
mixture was refluxed for 2 hours, then 4.3 g of 1,4-  
dihydro-2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-  
10 pyridine-3-carboxylic acid was added thereto, under an  
ice-cooled and stirred condition while the reaction  
mixture was as in a suspended state, 1.7 g of 3-p-(2-  
tetrahydropyranloxy)phenylpropargyl alcohol in 10 ml of  
anhydrous methylene chloride solution was added to the  
15 suspension and the whole mixture was stirred at a room  
temperature for 3 hours. Under an ice-cooled condition,  
the reaction mixture was poured in 1N-hydrochloric acid,  
and the organic layer was washed with water in three  
times and dried with anhydrous sodium sulfate, then  
20 solvent was removed by evaporation. The residue thus  
obtained was purified by means of a silica gel column  
chromatography (eluent: chloroform) to yield 2.8 g of  
methyl 3-[4-(2-tetrahydropyranloxyphenyl)]-2-propynyl  
1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-  
25 dicarboxylate in the form of light yellow indefinite  
form crystals.

1 Example 4

2.7 Grams of methyl 3-[4-( $\alpha$ -tetrahydropyranloxy-phenyl)]-2-propynyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate was dissolved in 5 30 ml of methanol, then 10 mg of p-toluenesulfinic acid was added and the mixture was stirred for 1 hour. The reaction mixture was neutralized by adding a saturated sodium hydrogen carbonate aqueous solution, further 100 ml of water was added then the mixture was extracted with 10 chloroform. The chloroform layer was washed with water in three times, then dried with anhydrous sodium sulfate, the solvent was removed by evaporation. The residue thus obtained was purified by means of a silica gel column chromatography (eluent: ethyl acetate:n-hexane = 4:1), 15 next recrystallized from tetrahydrofuran-n-hexane to yield 1.2 g of methyl 3-(4-hydroxyphenyl)-2-propynyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate in the form of yellow prism-like crystals. Melting point: 173 - 176°C.

20 Example 5

To a mixture consisting of 1.9 of 1,4-dihydro-2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)pyridine-3-carboxylic acid, 0.78 ml of 30% sodium hydroxide aqueous solution and 15 ml of HMPA were added dropwise 1.5 g of 25 4-(4-methylthiophenyl)-3(E)-butenyl bromide. The mixture was stirred at a room temperature for 8 hours, then at 40 - 45°C for 5 hours, next the reaction mixture was

1 poured into an ice-water and extracted with chloroform. The chloroform layer was washed with water, then dried with anhydrous sodium sulfate, and the solvent was removed by evaporation. The residue thus obtained was  
5 purified by means of a silica gel column chromatography (eluent: ethyl acetate:n-hexane = 1:2), recrystallization from ethyl acetate-n-hexane to yield 1.0 g of methyl 4-(4-methylthiophenyl)-3(E)-butenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate in  
10 the form of light yellow powdery substance. Melting point: 165 - 170°C.

Example 6

3.36 Grams of 1-[2(E)-acetoacetocymethylvinyl]-4-(2-tetrahydropyranloxy)benzene, 1.5 g of 3-nitrobenzaldehyde and 1.2 g of methyl 3-aminocrotonate were added to 20 ml of isopropanol, and the mixture was refluxed for 8 hours. The reaction mixture was concentrated and the residue was purified by means of a silica gel column chromatography (eluent: chloroform)  
15 to yield 1.2 g of methyl 3-(4-tetrahydropyranloxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate.

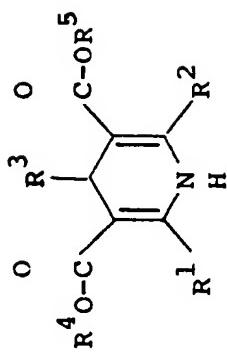
N. M. R. δ (CDCl<sub>3</sub>):

1.4 - 2.0 (6H, m), 2.26 (6H, m), 3.53 (3H, s),  
3.4 - 4.0 (2H, m), 4.58 (2H, d, J=6Hz), 5.03  
(1H, s), 5.30 (1H, t, J=3Hz), 5.97 (1H, dt,  
Ja=6Hz, Jb=16Hz), 6.30 (1H, bs), 6.37 (1H, d,

J=16Hz), 6.88 (2H, d, J=9Hz), 7.14 (2H, d,  
J=9Hz), 7.20 (1H, t, J=6Hz), 7.50 (1H, dt,  
Ja=2Hz, Jb=6Hz), 7.82 (1H, dt, Ja=2Hz, Jb=6Hz),  
8.00 (1H, t, J=2Hz).

1 Examples 7 - 30

By using a suitable starting material, and by methods similar to those described in Examples 1 and 6, there were prepared compounds as shown in Table 1 as follows.

Table 1

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Melting point (°C) (Recrystallization solvent)	Crystal form	Salt
7	CH <sub>3</sub>	CH <sub>3</sub>	-C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub>	CH <sub>3</sub>	-OH -C <sub>6</sub> H <sub>4</sub> -H -CH <sub>2</sub>	137.5 - 139 (Ether-benzene)	Yellow powdery crystals IR <sup>1</sup> )	-
8	CH <sub>3</sub>	CH <sub>3</sub>	-C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub>	CH <sub>3</sub>	-OH -C <sub>6</sub> H <sub>4</sub> -H -CH <sub>2</sub>	60 - 63 (Ether-n-hexane)	Light yellow powdery crystals	-
9	CH <sub>3</sub>	CH <sub>3</sub>	-C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub>	CH <sub>3</sub>	-OH -C <sub>6</sub> H <sub>4</sub> -H -CH <sub>2</sub>	75 - 105 (Ether-n-hexane)	Light yellow indefinite form crystals	-

(to be continued)

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- 90 -

(Continued)

Table 1

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Melting point (°C) (Recrystallization solvent)	Crystal form	Salt
1.0	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		181 - 182 (Methanol)	Yellow powdery crystals	-
1.1	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		173 - 176 (Tetrahydrofuran- n-hexane)	Yellow prism-like crystals	-
1.2	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		170 - 171 (Methanol)	Light yellow powdery crystals	-
1.3	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		90 - 95 (Tetrahydrofuran- n-hexane)	Light yellow indefinite form crystals	-

(to be continued)

(Continued)

Table 1

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Melting point (°C) (Recrystallization solvent)	Crystal form	Salt
14	CH <sub>3</sub>	CH <sub>3</sub>	Phenyl	CH <sub>3</sub>	OH	164 - 165 (Methanol- ether)	Light yellow powdery crystals	-
15	CH <sub>3</sub>	CH <sub>3</sub>	Phenyl	CH <sub>3</sub>	OH OCH <sub>3</sub>	146 - 153 (Isopropanol)	Yellow powdery crystals	-
16	CH <sub>3</sub>	CH <sub>3</sub>	Phenyl	NO <sub>2</sub>	CH <sub>3</sub> SCH <sub>3</sub>	165 - 170 (Ethyl acetate -n-hexane)	Light yellow indefinite form crystals	-
17	CH <sub>3</sub>	CH <sub>3</sub>	Phenyl	NO <sub>2</sub>	CH <sub>3</sub> SCH <sub>3</sub>	145 - 150 (Ethyl acetate -n-hexane)	Yellow indefinite form crystals	-

(to be continued)

(Continued)

Table 1

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Melting point (°C) (Recrystallization solvent)	Crystal form	Salt
18	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		68 - 70 (Ether-n-hexane)	Light yellow powdery crystals	-
19	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		NMR <sup>1)</sup>	Light yellow indefinite form crystals	-
20	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		NMR <sup>2)</sup>	Light yellow indefinite form crystals	-
21	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		NMR <sup>3)</sup>	Light yellow indefinite form crystals	-

(\*) OTHP: 2-tetrahydropyran-2-yloxy group  
(to be continued)

(Continued)

Table 1

Example No.	$R^1$	$R^2$	$R^3$	$R^4$	$R^5$	Melting Point ( $^{\circ}C$ ) (Recrystallization Solvent)	Crystal form	Salt
22	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		NMR <sup>4</sup>	Light yellow indefinite form crystals	-
23	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		NMR <sup>5</sup>	Light yellow indefinite form crystals	-
24	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		NMR <sup>6</sup>	Light yellow indefinite form crystals	-
25	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		NMR <sup>7</sup>	Yellow indefinite form crystals	-

(\*) OTHP: 2-tetrahydropyranoyloxy group

(to be continued)

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(continued)

Table 1

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Melting point (°C) (Recrystallization solvent)	Crystal form	Salt
26	CH <sub>3</sub>	CH <sub>3</sub>	CF <sub>3</sub>	CH <sub>3</sub>	-CH <sub>2</sub> —O <sup>(*)</sup> THP	NMR <sup>8)</sup>	Light yellow indefinite form crystals	-
27	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>	CH <sub>3</sub>	-CH <sub>2</sub> —O <sup>(*)</sup> CH <sub>3</sub>	NMR <sup>9)</sup>	Light yellow indefinite form crystals	-
28	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>	CH <sub>3</sub>	OCH <sub>2</sub> OC <sub>2</sub> H <sub>5</sub>	NMR <sup>10)</sup>	Light yellow indefinite form crystals	-
29	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>	CH <sub>3</sub>	Cl	120.5 - 121.5 (Tetrahydrofuran- n-hexane)	Yellow powdery crystals	-

(\*) OTHP: 2-tetrahydropyranoyloxy group

(to be continued)

(Continued)

Table 1

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Melting point (°C) (Recrystallization solvent)	Crystal form	Salt
30	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		122 - 124 (Tetrahydrofuran- n-hexane)	Light yellow powdery crystals	-
31	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		92 - 95 (Chloroform- n-hexane)	Light yellow powdery crystals	-
32	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		NMR 1.2) <sup>(*)</sup> OTHP	Yellow oily substance	-
33	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		170 - 172 (Ether- n-hexane)	Light yellow prism-like crystals	-

(\*) OTHP: 2-tetrahydropyranoyloxy group

(to be continued).

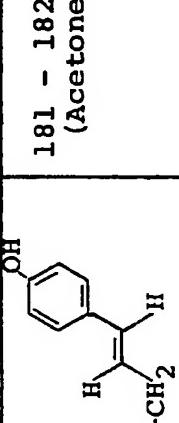
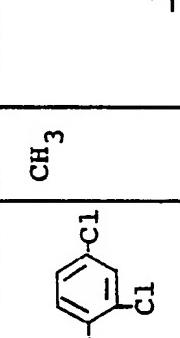
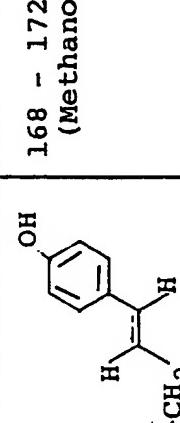
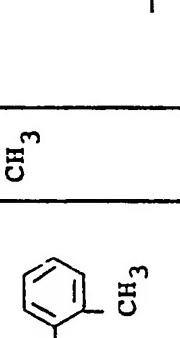
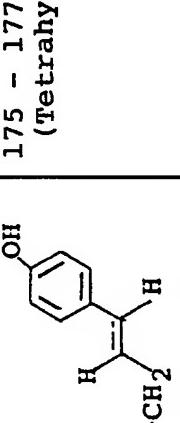
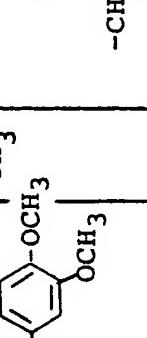
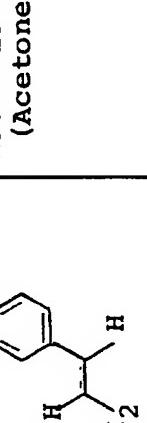
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Table 1

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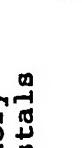
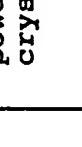
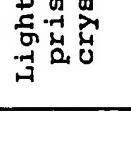
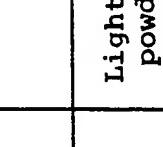
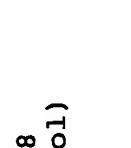
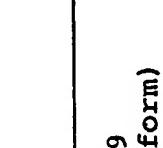
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Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Melting point (°C) (Recrystallization solvent)	Crystal form	Salt
34	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		181 - 182 (Acetone)	Light yellow prism-like crystals	-
35	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		168 - 172 (Methanol)	Light yellow powdery crystals	-
36	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		175 - 177 (Tetrahydrofuran)	Light yellow powdery crystals	-
37	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		197 - 198 (Acetone)	Light yellow powdery crystals	-

(to be continued)

(Continued)

Table 1

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Melting point (°C) (Recrystallization solvent)	Crystal form	Salt
38	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		102.5 - 105 (Methylene chloride)	Light yellow powdery crystals	-
39	CH <sub>3</sub>	CH <sub>3</sub>		C <sub>2</sub> H <sub>5</sub>		145 - 148 (Methanol)	Light yellow prism-like crystals	-
40	CH <sub>3</sub>	CH <sub>3</sub>				158 - 159 (Chloroform)	Light yellow powdery crystals	-
41	CH <sub>3</sub>			CH <sub>3</sub>		121 - 122 (Ether)	Light yellow powdery crystals	-

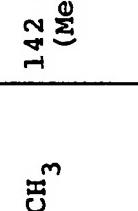
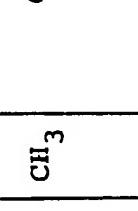
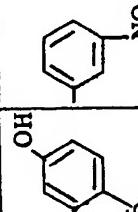
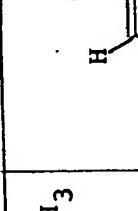
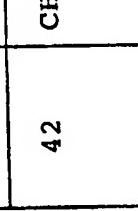
(to be continued)

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(Continued)

Table 1

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Melting point (°C) (Recrystallization solvent)	Crystal form	Salt
42	CH <sub>3</sub>			CH <sub>3</sub>	CH <sub>3</sub>	142 - 145 (Methanol)	Light yellow	1/2 · H <sub>2</sub> O
43	CH <sub>3</sub>			CH <sub>3</sub>	CH <sub>3</sub>	137 - 140 (Methanol)	Yellow powdery crystals	1/2 · H <sub>2</sub> O
44	CH <sub>3</sub>			CH <sub>3</sub>	CH <sub>3</sub>	101.5 - 115 (Ethyl acetate- ether) NMR 13)	Yellow powdery crystals	HCl · H <sub>2</sub> O
45	CH <sub>3</sub>			CH <sub>3</sub>		194 - 196 (Methanol)	Light yellow needle-like crystals	-

(to be continued)

(Continued)

Table 1

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Melting point (°C) (Recrystallization solvent)	Crystal form	Salt
46	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		157 - 158 (Methanol)	Light yellow needle-like crystals	-
47	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		75 - 90 (Ether- n-hexane) NMR 14)	Light yellow powdery crystals	-
48	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>		82 - 85 (Ether- n-hexane)	Light yellow powdery crystals	-

(to be continued)

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(Continued)

Table 1

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Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Melting point (°C) (Recrystallization solvent)	Crystal form	Salt
49	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>	-CH <sub>2</sub> CH <sub>2</sub> NCH <sub>2</sub> C≡C-		96 - 102 (Ether-n-hexane)	Light yellow powdery crystals
50	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>	-CH <sub>2</sub> CH <sub>2</sub> -S-CH <sub>2</sub>		81.5 - 83 (Ethyl acetate-diisopropyl ether)	Light yellow powdery crystals
51	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>	-CH <sub>2</sub> CH <sub>2</sub> -O-CH <sub>2</sub>		77.5 - 78.5 (Ethyl acetate-diisopropyl ether)	Light yellow powdery crystals
52	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>	-CH <sub>2</sub> CH <sub>2</sub> -S-CH <sub>2</sub> C≡C-		NMR <sup>15)</sup>	-

(to be continued)

(Continued)

Table 1

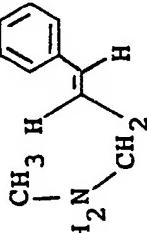
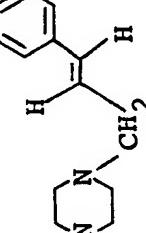
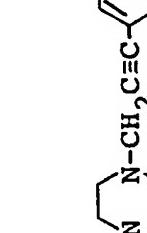
Example No.	$R^1$	$R^2$	$R^3$	$R^4$	$R^5$	Melting point ( $^{\circ}C$ ) (Recrystallization solvent)	Crystal form	Salt
53	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>	-CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> C≡C-		NMR 16)	Light yellow indefinite form crystals
54	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>	-CH <sub>2</sub> CH <sub>2</sub> -N		115 - 116 (Ethyl acetate- diisopropyl ether)	Light yellow powdery crystals
55	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>	-CH <sub>2</sub> CH <sub>2</sub> -N		115 - 116 (Ethyl acetate- diisopropyl ether)	Light yellow powdery crystals
56	CH <sub>3</sub>	CH <sub>3</sub>		CH <sub>3</sub>	-CH <sub>2</sub> CH <sub>2</sub> -N		168 - 169 (Acetone)	Light yellow powdery crystals

(to be continued)

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(Continued)

Table 1

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Melting point (°C) (Recrystallization solvent)	Crystal form	Salt
57	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>	CH <sub>3</sub>		NMR 17)	Yellow indefinite form crystals	-
58	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>	CH <sub>3</sub>		154 - 158 (Chloroform- n-hexane)	Light yellow powdery crystals	2HCl · H <sub>2</sub> O
59	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>	CH <sub>3</sub>		217 - 220 (Ethyl acetate- methanol- water)	Light yellow needle-like crystals	2HCl

(to be continued)

(Continued)

Table 1

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Melting point (°C) (Recrystallization solvent)	Crystal form	Salt
60	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>	CH <sub>3</sub>	-CH <sub>2</sub> C≡C- 	62 - 68 NMR 18)	Yellow indefinite form crystals	
61	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>	CH <sub>3</sub>	-CH <sub>2</sub> C≡C- 	144 - 146 (Diisopropyl ether- ethanol)	Light yellow powdery crystals	HCl
62	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>	CH <sub>3</sub>	 -CH <sub>2</sub> 'OC <sub>2</sub> H <sub>5</sub>	NMR 19	-	-

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IR<sup>1)</sup> 1660, 1680, 1700 cm<sup>-1</sup>

NMR<sup>1)</sup> (90MHz, CDCl<sub>3</sub>):

2.28 (3H, s), 2.35 (6H, s), 3.64 (3H, s), 4.67 (2H, d, J=7Hz), 5.12 (1H, s),  
6.06 (1H, broad, s), 6.15 (1H, d, t, Ja=7Hz, Jb=16Hz), 6.50 (1H, d, J=16Hz),  
7.03 (2H, d, J=8Hz), 7.30 (2H, d, J=8Hz), 7.32 (1H, t, J=8Hz), 7.63 (1H, dt,  
Ja=2Hz, Jb=8Hz), 7.97 (1H, d, t, Ja=2Hz, Jb=8Hz), 8.12 (1H, t, J=2Hz)

NMR<sup>2)</sup> (90MHz, CDCl<sub>3</sub>):

1.45-2.10 (6H, m), 2.30 (6H, t), 3.40-4.00 (2H, m), 3.56 (3H, s), 4.63 (2H, d,  
J=6Hz), 5.10 (1H, s), 5.37 (1H, t, J=3Hz), 6.17 (1H, d, t, Ja=6Hz, Jb=16Hz),  
6.45 (1H, d, J=16Hz), 6.65-7.20 (4H, m), 7.30 (1H, t, J=7Hz), 7.62 (1H, d, t,  
Ja=2Hz, Jb=7Hz), 7.95 (1H, d, t, Ja=2Hz, Jb=7Hz), 8.13 (1H, t, J=2Hz)

NMR<sup>3)</sup> (90MHz, CDCl<sub>3</sub>):

2.30 (3H, s), 2.32 (3H, s), 3.38 (3H, s), 3.53 (3H, s), 4.65 (2H, d, J=7Hz),  
5.10 (1H, s), 5.13 (2H, s), 6.20 (1H, dt, Ja=6Hz, Jb=16Hz), 6.47 (1H, s),  
6.87 (1H, d, J=16Hz), 6.87-7.48 (5H, m), 7.62 (1H, dt, Ja=2Hz, Jb=7Hz),  
7.93 (1H, dt, Ja=2Hz, Jb=7Hz), 8.12 (1H, t, J=2Hz)

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NMR<sup>4</sup>) (90MHz, CDCl<sub>3</sub>):

8.08 (1H, t, J=2Hz)

NMR<sup>5</sup>) (90MHz, CDCl<sub>3</sub>):

1.30-2.0 (6H, m), 2.32 (6H, s), 3.53 (3H, s), 3.3-3.95 (2H, m), 4.79 (2H, s),  
5.07 (1H, s), 5.33 (1H, t, J=3Hz), 6.02 (1H, s), 6.93 (2H, d, J=10Hz), 7.28  
(2H, d, J=10Hz), 7.27 (1H, t, J=8Hz), 7.66 (1H, d, J=8Hz), 7.93 (1H, d, J=8Hz),

8.10 (1H, s)

NMR<sup>6</sup>) (90MHz, CDCl<sub>3</sub>):

1.40-2.10 (6H, m), 2.32 (6H, s), 3.43 (3H, s), 3.20-3.85 (2H, m), 4.43 (2H, d,  
J=7Hz), 4.95 (1H, s), 5.23 (1H, t, J=3Hz), 5.04-5.80 (1H, m), 5.93-6.53 (3H, m),  
6.60 (1H, s), 6.87 (2H, d, J=10Hz), 7.20 (2H, d, J=10Hz), 7.23 (1H, t, J=8Hz),  
7.53 (1H, d, t, Ja=2Hz, Jb=8Hz), 7.88 (H, d, t, Ja=2Hz, Jb=8Hz)

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NMR<sup>7</sup>) (60MHz, CDCl<sub>3</sub>):

1.40-2.0 (6H, m), 2.30 (3H, s), 2.33 (3H, s), 3.20-3.90 (2H, m), 3.60 (3H, s),  
4.63 (2H, d, J=6Hz), 5.37 (1H, t, J=3Hz), 5.80 (1H, s), 6.03 (1H, d, t, Ja=6Hz,  
Jb=16Hz), 6.80 (1H, s), 6.38 (1H, d, J=16Hz), 6.90 (2H, d, J=9Hz), 7.20 (2H,  
d, J=9Hz), 6.75-7.80 (4H, m)

NMR<sup>8</sup>) (90MHz, CDCl<sub>3</sub>):

1.43-2.15 (6H, m), 2.30 (6H, s), 3.38 (3H, s), 3.20-3.80 (2H, m), 4.47 (2H, dd,  
Ja=3Hz, Jb=7Hz), 5.23 (1H, t, J=3Hz), 5.43 (1H, s), 6.83 (1H, broad, s), 5.94  
(1H, dt, Ja=6Hz, Jb=16Hz), 6.23 (1H, d, J=16Hz), 6.87 (2H, d, J=9Hz), 7.13 (2H,  
d, J=9Hz), 6.75-7.60 (4H, m)

NMR<sup>9</sup>) (90MHz, CDCl<sub>3</sub>):

1.5-2.1 (6H, m), 2.28 (3H, s), 3.53 (3H, s), 3.76 (3H, s), 3.4-4.1 (1H, m),  
4.57 (2H, d, J=6Hz), 5.27 (1H, t, J=3Hz), 5.99 (1H, dt, Ja=6Hz, Jb=16Hz),  
6.07 (1H, s), 6.36 (1H, d, J=16Hz), 6.73 (1H, d, J=7Hz), 6.78 (1H, s), 6.93  
(1H, D, J=7Hz), 7.18 (1H, t, J=7Hz), 7.50 (1H, dt, Ja=2Hz, Jb=7Hz), 7.83  
(1H, dt, Ja=2Hz, Jb=7Hz), 7.99 (1H, t, J=2Hz)

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NMR<sup>10</sup> (60MHz, CDCl<sub>3</sub>):

1.24 (3H, t, J=7Hz), 2.37 (3H, s), 3.66 (3H, s), 3.79 (2H, q, J=7Hz), 4.70 (2H, d, J=6Hz), 5.16 (1H, s), 5.30 (2H, s), 5.91 (1H, broad, s), 6.10 (1H, dt, Ja=6Hz, Jb=16Hz), 6.40 (1H, d, J=16Hz), 7.00-7.47 (4H, m), 7.64 (1H, dt, Ja=2Hz, Jb=7Hz), 7.97 (1H, dt, Ja=2Hz, Jb=7Hz), 8.14 (1H, t, J=2Hz)

NMR<sup>11</sup> (90MHz, CDCl<sub>3</sub>):

1.40-2.10 (6H, m), 2.26 (6H, m), 3.53 (3H, s), 3.40-4.0 (2H, m), 4.58 (2H, d, J=6Hz), 5.03 (1H, s), 5.30 (1H, t, J=3Hz), 5.97 (1H, dt, Ja=6Hz, Jb=16Hz), 6.30 (1H, broad, s), 6.37 (1H, d, J=16Hz), 6.88 (2H, d, J=9Hz), 7.14 (2H, d, J=9Hz), 7.20 (1H, t, J=6Hz), 7.50 (1H, dt, Ja=2Hz, Jb=6Hz), 7.82 (1H, dt, Ja=2Hz, Jb=6Hz), 8.00 (1H, t, J=2Hz)

NMR<sup>12</sup> (90MHz, CDCl<sub>3</sub>):

1.5-2.1 (6H, m), 2.33 (6H, s), 2.48 (2H, q, J=6Hz), 3.58 (3H, s), 3.5-4.0 (2H, m), 4.15 (2H, t, J=6Hz), 5.09 (1H, s), 5.40 (1H, m), 5.93 (1H, d, t, J=15Hz, 6Hz), 6.30 (1H, s), 6.32 (1H, d, J=15Hz), 6.96 (2H, d, J=9Hz), 7.19 (2H, d, J=9Hz), 7.1-7.3 (1H, m), 7.5-7.7 (1H, d, m, J=6Hz), 7.8-8.0 (1H, D, m, J=6Hz), 8.10 (1H, m)

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- NMR<sup>13</sup>) (90MHz, CDCl<sub>3</sub>):  
2.36 (3H, s), 2.40 (3H, s), 3.25 (2H, d, J=6Hz), 3.63 (6H, s), 3.6-3.9 (2H),  
5.10 (1H, s), 6.20 (1H, dt, J=16Hz, 6Hz), 6.53 (1H, d, J=16Hz), 7.1-8.3 (10H, m)
- NMR<sup>14</sup>) (90MHz, CDCl<sub>3</sub>):  
2.36 (9H, s), 2.75 (2H, t, J=6Hz) 3.53 (2H, s), 3.62 (3H, s), 4.16 (2H, t,  
J=6Hz), 5.11 (1H, s), 5.75 (1H, bs), 7.20-8.20 (9H, m)
- NMR<sup>15</sup>) (90MHz, CDCl<sub>3</sub>):  
2.33 (6H, s), 2.93 (2H, t, J=6Hz), 3.48 (2H, s), 3.63 (3H, s), 4.30 (2H, t,  
J=6Hz), 5.11 (1H, s), 6.22 (1H, s), 7.20-7.50 (6H, m), 7.66 (1H, dt, J=8Hz,  
J=2Hz), 7.93 (1H, bd, J=8Hz), 8.12 (1H, t, J=2Hz)
- NMR<sup>16</sup>) (90MHz, CDCl<sub>3</sub>):  
2.35 (6H, s), 3.60 (3H, s), 3.76 (2H, t, J=5Hz), 4.17-4.33 (2H, m), 4.36 (2H,  
s), 5.11 (1H, s), 5.80 (1H, bs), 7.20-8.20 (9H, m)
- NMR<sup>17</sup>) (90MHz, CDCl<sub>3</sub>):  
2.20 (3H, s), 2.27 (3H, s), 2.30 (3H, s), 2.62 (2H, t, J=6Hz), 3.51 (3H, s),  
4.18 (2H, m), 5.72 (1H, s), 5.82 (1H, bs), 6.18 (1H, dt, J=6Hz, J=16Hz),  
6.43 (1H, d, J=16Hz), 7.10-7.55 (8H, m), 7.62 (1H, d, J=7.5Hz)

NMR<sup>18</sup>) (90MHz, CDCl<sub>3</sub>):

2.37 (6H, s), 3.64 (3H, s), 4.87 (2H, s), 5.13 (1H, s), 6.20 (1H, brs),  
6.94 (1H, dd, J=4.5Hz, J=4Hz), 7.1-7.4 (3H, m), 7.64 (1H, d-m, J=8Hz)  
7.97 (1H, d-m J=8Hz), 8.10 (1H, t, J=2Hz)

NMR<sup>19</sup>) (90MHz CDCl<sub>3</sub>):

1.17 (3H, t, J=7Hz), 1.47 (3H, d, J=5.5Hz), 2.34 (6H, s), 3.35-3.95 (2H, m),  
3.60 (3H, s), 4.65 (2H, d= 6Hz), 5.10 (1H, s), 5.35 (1H, 2, J=5.2Hz),  
6.05 (1H, dt, J=6Hz, 15.5Hz), 6.46 (1H, d, J=15,5Hz), 6.89 (2H, d, J=9Hz),  
7.18-8.09 (6H, m)

1 Example 63

By using suitable starting materials, by a method similar to that described in Example 3, there were prepared compounds of Examples 1 and 7 - 62.

5 Example 64

By using suitable starting materials, by a method similar to that described in Example 5, there were prepared compounds of Examples 1 and 7 - 15, and 17 - 62.

Example 65

- 10 0.5 Gram of methyl 3-(4-hydroxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate was dissolved in 5 ml of pyridine, then to this solution was added 0.5 ml of acetic anhydride under an ice-cooling condition. The  
15 reaction mixture was allowed to stand overnight, then poured into an ice-water, and extracted with ether. The ether layer was washed with a diluted hydrochloric acid, 10%-sodium bicarbonate aqueous solution and water in this order, then dried with anhydrous sodium sulfate.  
20 The ether extract was concentrate, and the residue thus obtained was purified by means of a silica gel column chromatography (eluent: methanol:chloroform=1:100) to yield 0.4 g of methyl 3-(4-acetoxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-  
25 pyridine-3,5-dicarboxylate in the form of light yellow indefinite form crystals.

NMR

2.28 (3H, s), 2.35 (6H, s), 3.64 (3H, s),  
4.67 (2H, d, J=7Hz), 5.12 (1H, s), 6.06  
(1H, broad S), 6.15 (1H, d, t, Ja=7Hz,  
Jb=16Hz), 6.50 (1H, d, J=16Hz), 7.03 (2H,  
d, J=8Hz), 7.30 (2H, d, J=8Hz), 7.32 (1H,  
t, J=8Hz), 7.63 (1H, dt, Ja=2Hz, Jb=8Hz),  
7.97 (1H, d, t, Ja=2Hz, Jb=8Hz), 8.12 (1H,  
t, J=2Hz)

1 Example 66

50 Grams of 4-(1-ethoxyethoxy)cinnamyl methyl  
2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine was  
dissolved in 600 ml of tetrahydrofuran, the solution  
5 was cooled to 5°C, then 170 ml of 0.5N-hydrochloric acid  
was added in one time to the solution. After 1 hour, the  
temperature of the reaction mixture was kept at 10-15°C,  
and the reaction mixture was stirred for 2 hours. Sodium  
chloride was added to the reaction mixture and the  
10 aqueous layer was removed, the 5%-sodium hydrogen carbonate  
aqueous solution was added to adjust the pH to 7.0-7.5.  
The aqueous layer was removed by separation, then the  
organic layer was washed with water, a saturated sodium  
chloride aqueous solution in the order, and dried with  
15 anhydrous magnesium sulfate. The dried organic layer was  
concentrated at 20-25°C, the residue thus obtained was  
recrystallized from chloroform to yield 20 g of (4-hydroxy-  
phenyl)-2(E)-propenyl methyl 2,6-dimethyl-4-(3-

1 nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

Melting point: 145.8 - 149.4°C.

IR: 1670 cm<sup>-1</sup>

In the above-mentioned Examples 66, the recrystallization was conducted by using ether in place of chloroform, there was yield (4-hydroxyphenyl)-2(E)-propenyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate having the melting point of 163-164°C.

IR: 1660 cm<sup>-1</sup>, 1680 cm<sup>-1</sup>.

10 Example 67

3.0 Grams of 3-nitrobenzaldehyde, 2.3 g of methyl 3-aminocrotonate and 5 g of methyl 4(E)-cinnamyloxy-acetoacetate were suspended in 15 ml of isopropanol, and the suspension was refluxed for 10 hours. After the reaction was finished, the solvent was removed by evaporation under a reduced pressure, and the residue thus obtained was purified by means of a silica gel column chromatography (eluent: ether:n-hexane = 1:3 to 1:2).

Recrystallization from ether to yield 4.0 g of 3,5-dimethyl 2-cinnamyloxy-6-methyl-4-(3-nitrophenyl)-3,5-dicarboxylate in the form of light yellow powdery substance. Melting point: 121 - 122°C.

By a method similar to that described in Example 67, and by using suitable starting materials, there were prepared compounds of Examples 42-44.

1 Example 68

5.1 Grams of 2-iodomethyl methyl 2,6-dimethyl-  
4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate,  
and 3.8 g of 4-phenyl-1,2,3,6-tetrahydropyridine were  
5 dissolved in 10 ml of toluene, and the solution was  
refluxed for 6 hours. After the reaction mixture was  
allowed to stand to cooled at a room temperature, the  
crystals precipitated in the reaction mixture were removed  
by filtration, the filtrate was concentrated and the  
10 residue thus obtained was dissolved in chloroform. The  
chloroform layer was washed with a saturated sodium hydro-  
gen carbonate aqueous solution and water in this order,  
then dried with anhydrous sodium sulfate. Then the  
dried chloroform extract was concentrated by removing  
15 the solvent by evaporation, and the residue thus obtained  
was purified by means of a silica gel column chromatography  
(eluent: chloroform:methanol = 300:1), and recrystallized  
from ethyl acetate-diisopropyl ether to yield 3.6 g of  
methyl 2-(4-phenyl-1,2,3,6-tetrahydropyridyl)ethyl 2,6-  
20 dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-  
dicarboxylate in the form of light yellow powdery sub-  
stance. Melting point: 115 - 116°C.

By a method similar to that described in  
Example 68, and by using suitable starting materials,  
25 there were prepared compounds of Examples 47 - 59.

Example 69

10.2 Grams of methyl 2-piperazinylethyl 2,6-

1 dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and 4.5 g of 3-phenylpropargyl bromide in 100 ml of acetonitrile were stirred at 30°C for 5 hours under heating condition. After the reaction was 5 finished, chloroform was added to the reaction mixture, and the mixture was washed with a saturated sodium hydrogen carbonate aqueous solution and water in this order, and dried with anhydrous sodium sulfate. The dried chloroform extract was concentrated by removing 10 the solvent by evaporation, the residue thus obtained was purified by means of a silica gel column chromatography (eluent: dichloromethane - methanol:dichloromethane = 1:100). The product thus purified was then converted into a hydrochloride by adding hydrochloric acid-dioxane, 15 and recrystallized from ethyl acetate-methanol-water to yield 1.2 g of methyl 2-[4-(3-phenyl-2-propynyl)-1-piperazinyl]ethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate in the form of light yellow needle-like crystals. Melting point: 217 - 220°C.

20 By a method similar to that described in Example 69, and by using a suitable starting material, there was prepared a compound of Example 58.

#### Pharmacological tests

The results of the pharmacological test on 25 dihydropyridine derivatives of the present invention are shown below.

The test compounds used in the tests are as

1 follows.

Test  
Compound  
No.

1. Methyl 3-(4-hydroxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate
2. Methyl 3-phenyl-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate
3. Methyl 5-(4-hydroxyphenyl)-2(E),4(E)-pentadienyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate
4. Methyl 3-methyl-3-(4-hydroxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate
5. Methyl 3-phenyl-2-propynyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate
6. Methyl 3-phenylpropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate [Reference compound: Japanese Patent Application Kokai (Laid-open) No. 56-36455 (1981)]
7. Methyl 3-(3-methoxy-4-hydroxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate
8. Methyl 3-(4-methoxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dihydrocarboxylate
9. Methyl 3-(1-methyl-1,2,3,4-tetrazol-5-yl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate
10. Methyl 3-furyl-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate
11. Methyl 3-(3-chloro-4-hydroxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate
12. Methyl 3-(4-hydroxyphenyl)-2-propynyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate

13. Methyl 3-(2-hydroxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate
14. Methyl 3-(4-hydroxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(2-trifluoromethylphenyl)pyridine-3,5-dicarboxylate
15. Methyl 4-(4-methylthiophenyl)-3(E)-butenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate
16. Methyl 3-(4-acetoxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate
17. Methyl 2-[4-(4-methylphenyl)-1,2,3,6-tetrahydropyridyl]ethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate
18. Methyl 3-(4-hydroxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate
19. Methyl 3-(4-hydroxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(2-methylphenyl)-pyridine-3,5-dicarboxylate
20. Methyl 3-(4-hydroxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3,4-dimethoxyphenyl)pyridine-3,5-dicarboxylate
21. Dimethyl 1,4-dihydro-2-[3-(4-hydroxyphenyl)-2(E)-propenylmethoxyethyl]-6-methyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate
22. Methyl 3-(2-thienyl)-2-propynyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate
23. Methyl 2-[4-(3-phenyl-2-propynyl)-1-piperazinyl]ethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate
24. Methyl 3-(4-hydroxyphenyl)-2(E)propenyl 1,4-dihydro-2,6-dimethyl-4-(2,4-dichlorophenyl)pyridine-3,5-dicarboxylate
25. Methyl 3-(3-hydroxyphenyl)-2(E)propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate
26. Methyl 2-(N-methyl-N-benzylamino)ethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate [Reference compound known as "Nicardipine"]

1 Pharmacological test-1

Vasodilative effects of the dihydropyridine derivatives of the present invention were determined by measuring the systolic blood pressures of test animals before and after the administration of test compound.

Systolic blood pressures and heart beat of SHR-rats (spontaneously hypertensive rats) were determined by a "tail cuff method". Thus the test animal was placed in a thermostat chamber (Type: FR-12RS, manufactured by Isuze & Co.) and was warmed at 40°C for 15 minutes so as to vasodilate the tail arteria, the systolic blood pressures were measured by an electro sphygmomanometer (Type: PE-300, manufactured by Narco-Biosystems, Inc.) and recorded by an ink-writing recorder (Type: RECTI-HORIZ 8s, manufactured by San-Ei Instrument & Co.). The experiments were conducted under non-anesthetized and semi-confinement conditions. The test compound was orally administered forcedly by using a sonde for oral administration. The test compound was suspended in 0.15%-gum arabic powder aqueous solution so as to make the quantity of the test compound to 2.5 ml/kg. The test animal was not fasted, and the systolic blood pressures (mm-Hg) were measured before the administration (hereinafter referred to as "PRE") and after the administration (8, 24, 30, 48, 54 and 72 hours after the administration) of the test compound. The data of systolic blood pressure measured before the

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1 administration are shown in absolute value of mmHg, and the data measured after the administration are shown in the differences from the absolute values. The results are shown in Table 2 as follows.

Table 2

Test Compound No.	Dosage (mg/kg) P.O.	PRE	Blood pressure (mm-Hg)			
			8 24	After the adminis- tration 30	48	72 54
1	30	195.0	-	-41.0	-52.0	-19.8
2	30	187.4	-	-38.6	-21.2	-19.2
3	30	180.8	-	-31.0	-30.8	-12.6
4	30	184.4	-	-18.0	-25.8	-14.6
5	30	180.8	-	-75.4	-66.8	-10.6
6	30	185.0	-20.3	+1.8	-	-

1 As can be seen the data shown in Table 2, the  
vasodilative effects of the dihydropyridine derivatives  
of the present invention can be prolonged for certain  
length of period as compared with that of the reference  
5 compounds.

**Pharmacological tests**

Calmodulin (calcium-dependent modulator protein) inhibitory activity of each of the test compounds was determined by judging from the difference between IC<sub>50</sub> (50%-inhibitory concentration) of calmodulin inhibitory activity of the test compound being measured in the presence of calmodulin together with calmodulin-dependent cyclic-AMP phosphodiesterase, and another IC<sub>50</sub> of calmodulin-dependent cyclic-AMP phosphodiesterase inhibitory activity of the same test compound being measured in the absence of calmodulin. In other words, calmodulin-specific-inhibitory activity of each of the test compounds was determined in case that the test compound shows higher inhibitory activity against calmodulin-dependent cyclic-AMP phosphodiesterase in the presence of calmodulin than another inhibitory activity against calmodulin-dependent cyclic-AMP phosphodiesterase only.

1) Reagents used in the test

(1) Calmodulin: A calmodulin product manufactured by Amano & Co., which was isolated from the brain of bovine, and purified so as to be considered as a single substance with respect to SDS-page (poly-

1 acrylamide gel electrophoresis) method.

(2) Calmodulin-dependent cyclic-AMP phosphodiesterase (EC 3.1.4.17): An enzyme substance isolated from the heart of bovine and purified partially by a 5 method of modified version of the disclosure in H. C. Ho, T. S. Teo, et al.: "Biochim. Biophys. Acta", 429, 461 (1976).

(3) 5'-Nucleotidase (EC 3.1.3.5): Grade IV substance (isolated from Crotalus adamanteus venom)  
10 manufactured by Sigma & Co.

(4) Others: Remainder of the reagents used in the test were those of reagent grade chemicals manufactured by Wako Pure-Chemical Industries, Ltd.

2) Method for the test

15 Calmodulin inhibitory activity of each of the test compounds was measured by a method of modified version of the disclosure in T. S. Teo and T. H. Wang: "J. Bio. Chem.", 248, 588 (1973).

(1) Cyclic-AMP-phosphodiesterase: One unit 20 thereof hydrolyzes 1.0 micromole of 3':5'-cyclic-AMP to 5'-AMP per minute at pH 7.5 at 30°C, in the presence of a saturating level of calmodulin.

(2) Calmodulin: One unit thereof stimulates 25 0.015 activated unit of cyclic-AMP phosphodiesterase to 50% of the maximum activity of the enzyme.

(3) 5'-Nucleotidase: One unit thereof hydrolyzes 1.0 micromole of inorganic phosphorus from adenosine 5'-monophosphate per minute at pH 9.0 at 37°C.

1           3) Reactions in the tests

(1) Calmodulin-cyclic-AMP phosphodiesterase  
inhibitory activity:

40 mM of Imidazol, 20 mM of MgCl<sub>2</sub>,  
5 20 mM of CaCl<sub>2</sub>, 0.008 unit of cyclic-AMP phospho-  
diesterase, 1.0 unit of calmodulin, 0.2 unit of 5'-  
nucleotidase and 1.0 ml of 10 mM-tris(hydroxymethyl)amino-  
methane/HCl buffer solution (pH 7.0) containing 0.5 mM  
of cyclic-AMP were mixed together, and reacted at 30°C  
10 for 30 minutes. Each of the test compounds was dis-  
solved in methanol or N,N-dimethylformamide as the  
solvent, provided that the quantity of the solvent was  
not exceed 2% of the total amount of the mixture. After  
the reaction was completed, the reaction mixture was  
15 ice-cooled, and 0.5 ml each of aqueous solutions of  
16.5%-trichloroacetic acid, 1%-thiourea, 3%-ammonium  
ferrous sulfate were respectively added to the reaction  
mixture. Further, 0.15 ml of 4.4%-ammonium molybdate  
solution was added to the mixture and the whole of the  
20 mixture was stirred, and was centrifuged at 3,000 r.p.m.  
for 10 minutes. Then, the centrifuged mixture was  
allowed to stand at a room temperature for 20 minutes.  
The OD<sub>660 nm</sub> (optical density at 660 nm) was measured.

(2) Cyclic-AMP phosphodiesterase inhibitory  
25 activity:

The reaction was conducted by a method  
similar to that described in (1) as mentioned above,  
except that 1 mM of EGTA [ethylene glycol-bis(β-amino

1 ethyl ether)-N,N-tetraacetic acid] was used in place of 20 mM of CaCl<sub>2</sub>. The reaction was conducted for 3 hours. The results are shown in Table 3 as follows.

Table 3

Test Compound No.	Calmodulin-cyclic-AMP phosphodiesterase IC <sub>50</sub> (μg/ml)	Cyclic-AMP phosphodiesterase IC <sub>50</sub> (μg/ml)
1	4.1	60
2	2.5	>100
3	0.85	>100
7	5.2	86
8	2.7	>100
9	5.3	36
10	1.55	>100
11	5.3	100
12	0.78	13
13	1.65	12.5
14	6.25	>100
15	0.062	0.23
16	3.0	50
17	5.5	>100
18	6.8	32
19	5.8	58
20	3.2	30
21	6	>100
22	1.1	>100
23	8.0	>100
24	2.45	15

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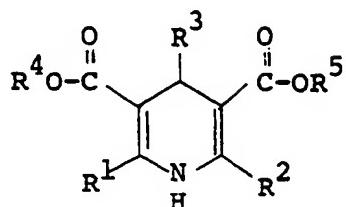
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25	0.9	24.6
26	6.25	13

1           As can be seen from the data shown in Table 3.  
the dihydropyridine derivatives of the present invention  
have specific inhibitory activity against calmodulin  
as compared with that of indicated by known compound.

WHAT IS CLAIMED IS:

1. A dihydropyridine derivative represented by the general formula,



wherein R<sup>1</sup> and R<sup>4</sup> are each a lower alkyl group; R<sup>2</sup> is a lower alkyl group or a group of the formula -CH<sub>2</sub>-A-R<sup>6</sup> [wherein A is a straight-chain or branched-chain unsaturated hydrocarbon residual group which may have an oxygen atom or a group of the formula -N-R<sup>7</sup> (wherein R<sup>7</sup> is a lower alkyl group); and R<sup>6</sup> is a phenyl group which may have a hydroxyl group]; R<sup>3</sup> is a phenyl group which may have 1 to 2 substituents selected from the group consisting of a nitro group, a lower alkyl group which may have 1 to 3 halogen atoms, a lower alkoxy group and a halogen atom; and R<sup>5</sup> is a lower alkyl group, a 1,2,3,6-tetrahydropyridyl-lower alkyl group which may have, as the substituent, a phenyl group which may have halogen atoms or lower alkyl groups as the substituents on the phenyl ring, or a group of the formula -CH<sub>2</sub>-A'-R<sup>8</sup> [wherein A' is a straight-chain or branched-chain unsaturated hydrocarbon residual group which may have or may not have an oxygen atom, a sulfur atom, a group of the formula -N-R<sup>7</sup> (wherein R<sup>7</sup> is a lower alkyl group),

or a group of the formula  $-\text{N}(\square)\text{N}-$  in the unsaturated hydrocarbon residual group; and  $\text{R}^8$  is a phenyl group which may have 1 to 3 substituents selected from the group consisting of a lower alkoxy group, a halogen atom, a lower alkylthio group, a hydroxyl group; a lower alkanoyloxy group, a tetrahydropyranyloxy group and a lower alkoxy-lower alkoxy group; a pyridyl group, a thienyl group, a furyl group, or a tetrazolyl group which may have a lower alkyl group as the substituent] provided that when  $\text{R}^5$  is a lower alkyl group, then  $\text{R}^2$  should be of a group of the formula  $-\text{CH}_2\text{-A-}\text{R}^6$  (wherein A and  $\text{R}^6$  are the same as defined above) or a salt thereof.

2. The dihydropyridine derivatives according to Claim 1, wherein  $\text{R}^2$  is a group of the formula  $-\text{CH}_2\text{-A-}\text{R}^6$  [wherein A is a straight-chain or branched-chain unsaturated hydrocarbon residual group having 2 to 6 carbon atoms in the unsaturated hydrocarbon residual moiety, having 1 to 3 double bonds and/or triple bonds therein, said unsaturated hydrocarbon residual group may have or may not have an oxygen atom or a group of the formula  $-\text{N-}\text{R}^7$  (wherein  $\text{R}^7$  is a lower alkyl group); and  $\text{R}^6$  is a phenyl group which may have a hydroxy group as the substituent].

3. The dihydropyridine derivatives according to Claim 1, wherein  $\text{R}^2$  is an alkyl group having 1 to 6 carbon atoms.

4. The dihydropyridine derivatives according to

Claim 2, wherein R<sup>5</sup> is an alkyl group having 1 to 6 carbon atoms.

5. The dihydropyridine derivatives according to Claim 3, wherein R<sup>5</sup> is a 1,2,3,6-tetrahydropyridyl-C<sub>1-6</sub>-alkyl group which may have, as the substituent on the pyridyl ring, a phenyl group which may have halogen atoms or lower alkyl groups as the substituents on the phenyl ring.

6. The dihydropyridine derivatives according to Claim 3, wherein R<sup>5</sup> is a group of the formula -CH<sub>2</sub>-A'-R<sup>8</sup> [wherein A' is a straight-chain or branched-chain unsaturated hydrocarbon residual group having 2 to 6 carbon atoms in the unsaturated hydrocarbon residual moiety, having 1 to 3 double bonds and/or triple bonds therein, said unsaturated hydrocarbon residual group may have or may not have an oxygen atom, a sulfur atom, a group of the formula -N-R<sup>7</sup> (wherein R<sup>7</sup> is a C<sub>1-6</sub>-alkyl group)], or a group of the formula -N-N- in the unsaturated hydrocarbon residual group.

7. The dihydropyridine derivatives according to Claim 2, wherein R<sup>5</sup> is a 1,2,3,6-tetrahydropyridyl-C<sub>1-6</sub>-alkyl group which may have, as the substituent on the pyridyl ring, a phenyl group which may have halogen atoms or C<sub>1-6</sub>-alkyl groups as the substituents on the phenyl ring; or a group of the formula -CH<sub>2</sub>-A'-R<sup>8</sup> (wherein A' and R<sup>8</sup> are the same as defined above)

8. The dihydropyridine derivatives according to Claim 6, wherein A' is a straight-chain or branched-chain

unsaturated hydrocarbon residual group having 2 to 6 carbons atoms in the unsaturated hydrocarbon residual moiety, which contains an oxygen atom, a sulfur atom, or a group of the formula  $-\text{N}-\text{R}^7$  (wherein  $\text{R}^7$  is  $\text{C}_{1-6}$ -alkyl group), or a group of the formula  $-\text{N}(\text{C}_6\text{H}_4)\text{N}-$  in the unsaturated hydrocarbon residual group.

9. The dihydropyridine derivatives according to Claim 6, wherein  $\text{A}'$  is a straight-chain or branched-chain unsaturated hydrocarbon residual group having 2 to 6 carbon atoms in the unsaturated hydrocarbon residual moiety, which does not contain an oxygen atom, a sulfur atom, or a group of the formula  $-\text{N}-\text{R}^7$  (wherein  $\text{R}^7$  is  $\text{C}_{1-6}$ -alkyl group), or a group of the formula  $-\text{N}(\text{C}_6\text{H}_4)\text{N}-$  in the unsaturated hydrocarbon residual group.

10. The dihydropyridine derivatives according to Claim 8, wherein  $\text{R}^8$  is a phenyl group which may have 1 to 3 substituents on the phenyl ring, selected from the group consisting of 2  $\text{C}_{1-6}$ -alkoxyl group, a halogen atom, a  $\text{C}_{1-6}$ -alkylthio group, a hydroxyl group,  $\text{C}_{1-6}$ -alkanoyloxy group, a tetrahydropyranyloxy group and  $\text{C}_{1-6}$ -alkoxy- $\text{C}_{1-6}$ -alkoxy group.

11. The dihydropyridine derivatives according to Claim 9, wherein  $\text{R}^8$  is a phenyl group which may have 1 to 3 substituents on the phenyl ring, selected from the group consisting of a  $\text{C}_{1-6}$ -alkoxy group, a halogen atom, a  $\text{C}_{1-6}$ -alkylthio group, a hydroxyl group, a  $\text{C}_{1-6}$ -alkanoyloxy group, a tetrahydropyranyloxy group and a  $\text{C}_{1-6}$ -alkoxy- $\text{C}_{1-6}$ -alkoxy group.

12. The dihydropyridine derivatives according to Claim 8 or 9, wherein R<sup>8</sup> is a pyridyl group, a thiienyl group, a furyl group, or a tetrazolyl group which may have a lower alkyl group as the substituent.

13. The dihydropyridine derivatives according to Claim 11, wherein R<sup>8</sup> is a phenyl group which may have 1 to 3 substituents on the phenyl ring, selected from the group consisting of a hydroxyl group and C<sub>1-6</sub>-alkanoyloxy group.

14. The dihydropyridine derivatives according to Claim 11, wherein R<sup>8</sup> is a phenyl group which contains 1 to 3 substituents on the phenyl ring, selected from the group consisting of a C<sub>1-6</sub>-alkoxy group, a halogen atom, a C<sub>1-6</sub>-alkylthio group, a tetrahydropyranylloxy group and C<sub>1-6</sub>-alkoxy-C<sub>1-6</sub>-alkoxy group.

15. The dihydropyridine derivatives according to Claim 13 or 14, wherein R<sup>3</sup> is a phenyl group which may have 1 to 2 nitro groups as the substituents on the phenyl ring.

16. The dihydropyridine derivatives according to Claim 13 or 14, wherein R<sup>3</sup> is a phenyl group having 1 to 2 C<sub>1-6</sub>-alkyl group as the substituents on the phenyl ring, said C<sub>1-6</sub>-alkyl group contains 1 to 3 halogen atoms as the substituents.

17. The dihydropyridine derivatives according to Claims 13 or 14, wherein R<sup>3</sup> is a phenyl group having 1 to 2 substituents on the phenyl ring, selected from the group consisting of a C<sub>1-6</sub>-alkyl group, a C<sub>1-6</sub>-alkoxy

group and a halogen atom.

18. The dihydropyridine derivatives according to Claim 15, wherein the straight-chain or branched-chain unsaturated hydrocarbon residual group is a straight-chain or branched-chain unsaturated hydrocarbon residual group which only contains 1 - 3 double bonds.

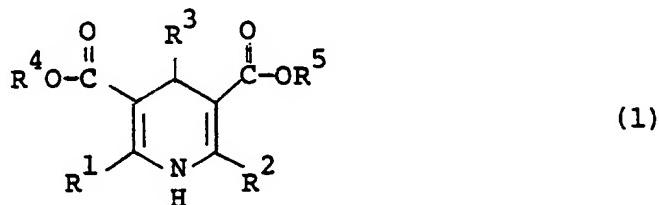
19. The dihydropyridine derivatives according to Claim 15, wherein the straight-chain or branched-chain unsaturated hydrocarbon residual group is a straight-chain or branched-chain unsaturated hydrocarbon residual group which only contains 1 - 3 triple bonds.

20. Methyl 3-(4-hydroxyphenyl)-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.

21. Methyl 3-phenyl-2(E)-propenyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.

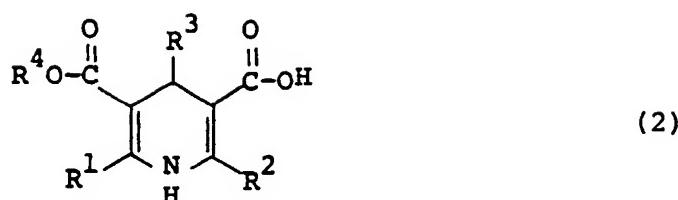
22. Methyl 3-phenyl-2-propynyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate.

23. A process for preparing a dihydropyridine derivative represented by the general formula (1),



[wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are the same as defined above], by reacting a compound represented by the

general formula (2),

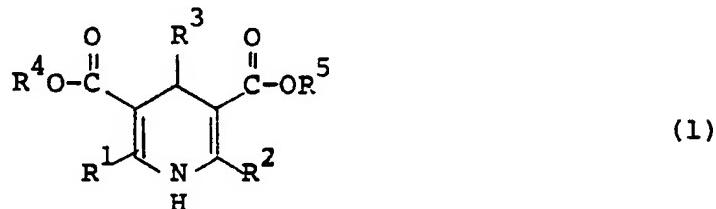


[wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are the same as defined above], with a compound represented by the general formula (3),



[wherein X is a hydroxyl group or a halogen atom].

24. A process for preparing a dihydropyridine derivative represented by the general formula (1),



[wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are the same as defined above], by reacting a compound represented by the general formula (4),



[wherein R<sup>2</sup> and R<sup>5</sup> are the same as defined above], with

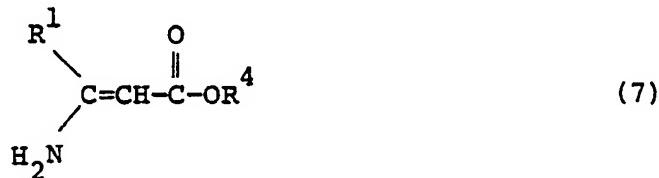
a compound represented by the general formula (5),



[wherein  $\text{R}^3$  is the same as defined above] to prepare a compound represented by the general formula

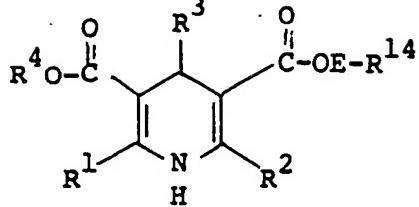


[wherein  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^5$  are the same as defined above], then thus prepared compound represented by the general formula (6) is reacted with a compound represented by the general formula (7),



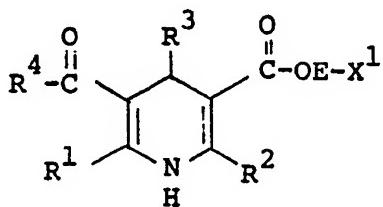
[wherein  $\text{R}^1$  and  $\text{R}^4$  are the same as defined above] to prepare the desired dihydropyridine derivative represented by the general formula (1).

25. A process for preparing a dihydropyridine derivative represented by the general formula (1a),



(1a)

[wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are the same as defined above; E is a lower alkylene group; R<sup>14</sup> is a 1,2,3,6-tetrahydropyridyl group which may have, as the substituent, a phenyl group which may have halogen atoms or lower alkyl groups as the substituents on the phenyl ring; or a group of the formula R<sup>6</sup>-(D')<sub>0</sub>-Y- (wherein R<sup>6</sup> is the same as defined above; D' is a saturated- or unsaturated-alkylene group; 0 is 0 or 1; Y is an oxygen atom, a sulfur atom, a group of the formula -N(R<sup>7</sup>)<sub>1</sub> (wherein R<sup>7</sup> is a lower alkyl group), or a group of the formula -N( N-), reacting a compound represented by the general formula (31),

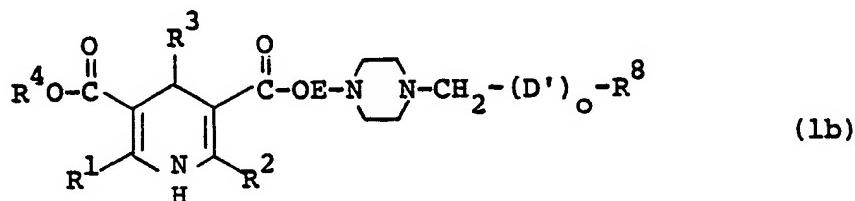


(31)

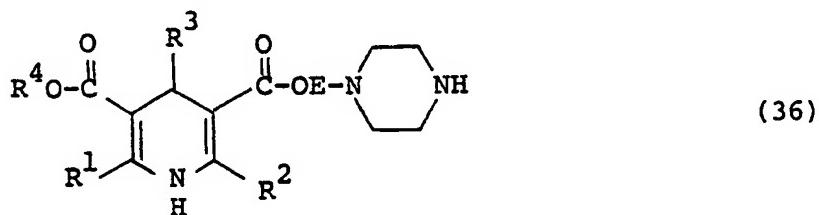
[wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and E are the same as defined above; and X<sup>1</sup> is a halogen atom] with a compound represented by the general formula (32),

[wherein R<sup>14</sup> is the same as defined above] to prepare the desired dihydropyridine derivative represented by the general formula (1a).

26. A process for preparing a dihydropyridine derivative represented by the general formula (1b),



[wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, D', E and R<sup>8</sup> are the same as defined above], by reacting a compound represented by the general formula (36),



[wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and E are the same as defined above], with a compound represented by the general formula (34a),



[wherein R<sup>8</sup> is the same as defined above; and X<sup>2</sup> is a halogen atom] to prepare the desire dihydropyridine derivative represented by the general formula (1b).

27. A hypotensive composition containing, as the active ingredient a dihydropyridine derivative represented by the general formula (1) as claimed in Claim 1 and pharmaceutically acceptable carriers.

28. A coronary blood flow improving composition containing, as the active ingredient a dihydropyridine derivative represented by the general formula (1) as claimed in Claim 1 and pharmaceutically acceptable carriers.